IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Hogan		
Serial No.:	09/976,423	Group No.:	1634
Filed:	10/21/2001	Examiner:	Goldberg
Entitled:	**METHODS AND COMPOSITIONS FOR PERIOPERATIVE GENOMIC PROFILING**		

APPELLANT'S BRIEF

APPEAL NO.:

EFS Web Filed
Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Dated: **April 15, 2009** By: /Thomas P. Vita, Jr./
Thomas P. Vita, Jr.

This Brief supports the appeal to the Board of Patent Appeals and Interferences from the Final Office Action dated March 24, 2008 in the application identified above, and is in furtherance of the Notice of Appeal filed September 15, 2008.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. HOGAN-06650. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)]:

I. REAL PARTY IN INTEREST

The real party in interest is the Inventor, Kirk Hogan, Madison, WI.

II. RELATED APPEALS AND INTERFERENCES

In an Appeal Brief filed November 9, 2005 in the present matter (Application Serial No. 09/976,423) the Appellant appealed the Final Office Action of May 10, 2005 (Appeal No. 2006-1517). A copy of the Decision on Appeal mailed July 31, 2006 is included in the RELATED PROCEEDINGS APPENDIX. The present application is a continuation-in-part of co-pending U.S. Application serial No. 09/613,887 that was the subject of Appeal No. 2006-1560. A copy of the Decision on Appeal mailed July 25, 2006 is included in the RELATED PROCEEDINGS APPENDIX.

III. STATUS OF CLAIMS

Claims 1-23 were filed in the original application. During prosecution of the application, claims 1-23 were cancelled and claims 24-44 were added in the Amendment and Response to Office Action filed January 8, 2003. Claims 24-44 were cancelled and claims 45-71 were added in the Amendment and Response to Office Action filed May 1, 2003. Claims 69 and 70 were cancelled in the Amendment and Response to Final Office Action filed July 7, 2004. Claims 45-68, and 71 were cancelled, and claims 72-107 were added in the Amendment and Response to Office Action filed February 17, 2005. Claims 72-107 were rejected in the Final Office Action dated May 10, 2005.

In an Appeal Brief filed November 9, 2005 the Applicant appealed the Final Office Action of May 10, 2005. In the Decision on Appeal mailed July 31, 2006 the Board of Patent Appeals and Interferences reversed all of the Examiner's rejections. The Office Action mailed September 12, 2006 was made in Response to the Board's rejections. Claims 108-112 were added in the Amendment and Response to Office Action of September 12, 2006. No other Claims are pending. Therefore, Claims 72-112 are pending in the application.

Appellant appeals the Final Office Action of March 24, 2008.

The Claims, as they now stand, are set forth in Section VIII. CLAIMS APPENDIX.

IV. STATUS OF AMENDMENTS

There are no pending amendments not entered into the record.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to kits for perioperative genomic screening of surgical subjects. In some embodiments, the present invention relates to kits for perioperative genomic screening for nucleic acid genetic markers indicative of responses to anesthesia, and to other perioperative or operative treatments and procedures, comprising, for example, reagents sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β.

In current clinical practice, there is no technology available that provides the information of the kits for generating perioperative genomic profiles of the present invention. In the past, screening tests of a patient's phenotype (*e.g.*, blood cell count and chemistries, urinalysis, electrocardiogram (EKG), and chest X-ray) were routinely performed prior to surgery. However, the present-day procedure for screening for susceptibility to heritable disorders of consequence in the interval surrounding surgery does not look at nucleic acid genetic markers, and is limited to asking a patient if they or their family members have had any previous difficulties with anesthesia or surgery. The use of laboratory phenotypic tests for patients prior to surgery has generally been reduced or eliminated. The reasons for elimination include the inaccuracy and lack of specificity of the various phenotypic tests, the aggregate costs of many different kinds of phenotypic screening tests necessary to assemble test panels, and uncertainty as to how to alter a treatment course of action in response to phenotypic test results. Accordingly, contemporary anesthesiology and surgery textbooks emphasize that recent studies indicate a lack of benefit from phenotypic testing as a method of assessing patients before surgery, and stress that cost-benefit strategies can only be justified when laboratory testing is reduced to that indicated by history-taking.

The kits for generating perioperative genomic profiles of the present invention stand in direct contrast to the history-taking and panels of phenotypic tests currently available and previously used. In the present invention, genetic alleles are tested in ensemble according to selection categories and criteria taught by the present invention, in order to construct a personalized perioperative genomic profile. The kits for generating perioperative genomic profiles of the present invention may be used, for example, to select the safest and most effective anesthetic regimen and surgical procedure, and to begin life-saving interventions as soon as possible. The kits for generating perioperative genomic profiles of the present invention thereby solve many of the problems described above that have led practitioners away from preoperative phenotypic testing. The kits for generating perioperative genomic profiles of the present invention are cost and time effective. As taught by the present invention, genomic markers are selected for inclusion in the profile by virtue of their analytical validity (*i.e.*, a high level of accuracy, specificity, and predictive value), their clinical validity (*i.e.*, a high level of correlation between DNA sequence variation and the trait of interest), and their clinical utility (*i.e.*, a significant impact of the test result on the patient's well-being during and after surgery). The kits for generating perioperative genomic profiles of the present invention thus allow for the individualization of treatment options for each subject undergoing a surgical procedure. In this fashion, the present invention provides a novel diagnostic tool currently unavailable in the surgical field, enabling solutions for problems that have no available alternatives. In the absence of any competing technology for quantifying subject's genetic contributors to perioperative risk, the present invention provides time-, cost-, and life-saving information to caregivers on an accelerated and amplified scale relative to current diagnostics.

In one embodiment of the present invention, a kit (described, for example, in the Specification at page 6, lines 15 – 20) for generating a perioperative genomic profile (described, for example, at page 3, lines 29 - 30, page 4, lines 7 - 12, page 18, lines 26 - 27, page 5, line 20, page 6, lines 15 - 20, page 8, lines 1 - 2, and lines 10 - 11, page 27, lines 13 – 17, and Figure 5) for a subject (described, for example, at page 29, lines 12 - 14), said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure (described, for example, at page 25, lines 25 - 30) is

described, comprising reagents (described, for example, at page 6, lines 20 - 21, page 19, lines 23 - 27, page 41, lines 4 - 5, page 45, lines 24 - 29, page 46, line 2, page 54, lines 27 - 28, and page 40, line 25 – page 49, line 2, "Assays for Generating Genomic Profiles") configured such that when exposed to a sample (described, for example, at page 29, line 4 – 11) containing target nucleic acid (described, for example, at page 11, lines 4 – 23) from a perioperative subject, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions (described, for example, at Figure 4 "Allele Panel", and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers") selected from the group consisting of *BChE* (described, for example, at page 6, lines 21 – 22), *CYP2D6* (described, for example, at page 6, lines 22 – 24), *F5* (described, for example, at page 6, lines 28 – 29), *F2* (described, for example, at page 6, line 2), *CACNAIS* (described, for example, at page 7, lines 1 – 2), *MTHFR* (described, for example, at page 6, line 26), *MTR* (described, for example, at page 6, lines 26 – 27), *CBS* (described, for example, at page 6 lines 27 – 28), *TNF*α (described, for example, at page 7, lines 3 – 4), and *TNF*β (described, for example, at page 7, line 4) (and described, for example, in Figure 5 "Detection of Allelic Variants"), so as to generate a genomic profile for use in selecting a perioperative course of action for said subject (described, for example, at page 3, line 30 – page 4, line 2, page 28, lines 9 – 13 and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers"), and a computer program (described, for example, at page 40, line 29 – page 41, line 5, page 49, lines 4 - 12 "Computer-Based Data Analysis", and page 50, lines 8 – 12), comprising instructions (described, for example, at page 6, lines 19 – 20) which direct a processor (described, for example, at page 50, line 19 – page 51, line 7) to analyze data derived from use of said reagents (described, for example, at page 49, line 14 – page 53, line 3, "Analysis and Delivery of Data").

In another embodiment of the present invention, a kit (described, for example, in the Specification at page 6, lines 15 – 20) for generating a perioperative genomic profile (described, for example, at page 3, lines 29 - 30, page 4, lines 7 - 12, page 18, lines 26 - 27, page 5, line 20, page 6, lines 15 - 20, page 8, lines 1 - 2, and lines 10 - 11, page 27, lines 13 – 17, and Figure 5) for a subject (described, for example, at page 29, lines 12 -

14), said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure (described, for example, at page 25, lines 25 - 30) is described, comprising reagents (described, for example, at page 6, lines 20 - 21, page 19, lines 23 - 27, page 41, lines 4 - 5, page 45, lines 24 - 29, page 46, line 2, page 54, lines 27 - 28, and page 40, line 25 – page 49, line 2, "Assays for Generating Genomic Profiles") configured such that when exposed to a sample (described, for example, at page 29, line 4 – 11) containing target nucleic acid (described, for example, at page 11, lines 4 – 23) from a perioperative subject, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions (described, for example, at Figure 4 "Allele Panel", and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers") selected from the group consisting of *BChE* (described, for example, at page 6, lines 21 – 22), *CYP2D6* (described, for example, at page 6, lines 22 – 24), *F5* (described, for example, at page 6, lines 28 – 29), *F2* (described, for example, at page 6, line 2), *CACNAIS* (described, for example, at page 7, lines 1 – 2), *MTHFR* (described, for example, at page 6, line 26), *MTR* (described, for example, at page 6, lines 26 – 27), *CBS* (described, for example, at page 6 lines 27 – 28), *TNF*α (described, for example, at page 7, lines 3 – 4), and *TNF*β (described, for example, at page 7, line 4) (and described, for example, in Figure 5 "Detection of Allelic Variants"), so as to generate a genomic profile for use in selecting a perioperative course of action for said subject (described, for example, at page 3, line 30 – page 4, line 2, page 28, lines 9 – 13 and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers"), and a computer program (described, for example, at page 40, line 29 – page 41, line 5, page 49, lines 4 - 12 "Computer-Based Data Analysis", and page 50, lines 8 – 12), comprising instructions (described, for example, at page 6, lines 19 – 20) which direct a processor (described, for example, at page 50, line 19 – page 51, line 7) to analyze data derived from use of said reagents (described, for example, at page 49, line 14 – page 53, line 3, "Analysis and Delivery of Data") to indicate an anesthesia treatment course of action (described, for example, at page 5, lines 7 - 8, page 6, lines 9 – 14).

In a further embodiment of the present invention, a kit (described, for example, in the Specification at page 6, lines 15 – 20) for generating a perioperative genomic profile

(described, for example, at page 3, lines 29 - 30, page 4, lines 7 - 12, page 18, lines 26 - 27, page 5, line 20, page 6, lines 15 - 20, page 8, lines 1 - 2, and lines 10 - 11, page 27, lines 13 – 17, and Figure 5) for a subject (described, for example, at page 29, lines 12 - 14), said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure (described, for example, at page 25, lines 25 - 30) is described, comprising reagents (described, for example, at page 6, lines 20 - 21, page 19, lines 23 - 27, page 41, lines 4 - 5, page 45, lines 24 - 29, page 46, line 2, page 54, lines 27 - 28, and page 40, line 25 – page 49, line 2, "Assays for Generating Genomic Profiles") configured such that when exposed to a sample (described, for example, at page 29, line 4 – 11) containing target nucleic acid (described, for example, at page 11, lines 4 – 23) from a perioperative subject, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions (described, for example, at Figure 4 "Allele Panel", and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers") selected from the group consisting of *BChE* (described, for example, at page 6, lines 21 – 22), *CYP2D6* (described, for example, at page 6, lines 22 – 24), *F5* (described, for example, at page 6, lines 28 – 29), *F2* (described, for example, at page 6, line 2), *CACNAIS* (described, for example, at page 7, lines 1 – 2), *MTHFR* (described, for example, at page 6, line 26), *MTR* (described, for example, at page 6, lines 26 – 27), *CBS* (described, for example, at page 6 lines 27 – 28), *TNF*α (described, for example, at page 7, lines 3 – 4), and *TNF*β (described, for example, at page 7, line 4) (and described, for example, in Figure 5 "Detection of Allelic Variants"), so as to generate a genomic profile for use in selecting a perioperative course of action for said subject (described, for example, at page 3, line 30 – page 4, line 2, page 28, lines 9 – 13 and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers"), and a computer program (described, for example, at page 40, line 29 – page 41, line 5, page 49, lines 4 - 12 "Computer-Based Data Analysis", and page 50, lines 8 – 12), comprising instructions (described, for example, at page 6, lines 19 – 20) which direct a processor (described, for example, at page 50, line 19 – page 51, line 7) to analyze data derived from use of said reagents (described, for example, at page 49, line 14 – page 53, line 3, "Analysis and Delivery of Data") to indicate a surgical treatment course of action (described, for

example, at page 3, lines 19 - 30, page 4, lines 22 - 23, page 6, lines 23 - 24, and page 9, lines 27 – 28).

In an additional embodiment of the present invention, a perioperative genomic profile (described, for example in the Specification, at page 3, lines 29 - 30, page 4, lines 7 - 12, page 18, lines 26 - 27, page 5, line 20, page 6, lines 15 - 20, page 8, lines 1 - 2, and lines 10 - 11, page 27, lines 13 – 17, and Figure 5) kit is described (described, for example, at page 6, lines 15 – 20) having component parts (described for example at page 19, lines 25 – 27, page 25, lines 21 – 24, and page 58, lines 16 –25)configured such that when exposed to a sample (described, for example, at page 29, line 4 – 11) containing target nucleic acid (described, for example, at page 11, lines 4 – 23) from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure (described, for example, at page 25, lines 25 - 30), are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions (described, for example, at Figure 4 "Allele Panel", and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers") selected from the group consisting of *BChE* (described, for example, at page 6, lines 21 – 22), *CYP2D6* (described, for example, at page 6, lines 22 – 24), *F5* (described, for example, at page 6, lines 28 – 29), *F2* (described, for example, at page 6, line 2), *CACNAIS* (described, for example, at page 7, lines 1 – 2), *MTHFR* (described, for example, at page 6, line 26), *MTR* (described, for example, at page 6, lines 26 – 27), *CBS* (described, for example, at page 6 lines 27 – 28), *TNF*α (described, for example, at page 7, lines 3 – 4), and *TNF*β (described, for example, at page 7, line 4) (and described, for example, in Figure 5 "Detection of Allelic Variants") to generate a genomic profile (described, for example, at page 3, lines 29 - 30, page 4, lines 7 - 12, page 18, lines 26 - 27, page 5, line 20, page 6, lines 15 - 20, page 8, lines 1 - 2, and lines 10 - 11, page 27, lines 13 – 17, and Figure 5) for use in selecting a perioperative course of action for said subject (described, for example, at page 3, line 30 – page 4, line 2, page 28, lines 9 – 13 and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers"), and thereby providing a subject-specific clinical pathway for said subject (described for example in Figure 1 "Alter Intervention" and Figure 3 "Therapeutic Plan"), comprising information to optimize perioperative care that, based at least on the

presence or absence of are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions (described, for example, at Figure 4 "Allele Panel", and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers") selected from the group consisting of *BChE* (described, for example, at page 6, lines 21 – 22), *CYP2D6* (described, for example, at page 6, lines 22 – 24), *F5* (described, for example, at page 6, lines 28 – 29), *F2* (described, for example, at page 6, line 2), *CACNAIS* (described, for example, at page 7, lines 1 – 2), *MTHFR* (described, for example, at page 6, line 26), *MTR* (described, for example, at page 6, lines 26 – 27), *CBS* (described, for example, at page 6 lines 27 – 28), *TNF*α (described, for example, at page 7, lines 3 – 4), and *TNF*β (described, for example, at page 7, line 4) (and described, for example, in Figure 5 "Detection of Allelic Variants") directs a user (described, for example, in Figure 1 "MD User Interpretation" and at page 10, lines 17 – 20, page 50, lines 8 – 18, page 50, line 19 – page 53, line 3, and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers"), to a specific clinical pathway of medical intervention for said subject (described, for example, at page 4, lines 16 – 24 and page 5, lines 4 - 6.)

In one embodiment of the present invention, a perioperative genomic profile (described, for example in the Specification, at page 3, lines 29 - 30, page 4, lines 7 - 12, page 18, lines 26 - 27, page 5, line 20, page 6, lines 15 - 20, page 8, lines 1 - 2, and lines 10 - 11, page 27, lines 13 – 17, and Figure 5) kit is described (described, for example, at page 6, lines 15 – 20) having component parts (described for example at page 19, lines 25 – 27, page 25, lines 21 – 24, and page 58, lines 16 –25) configured such that when exposed to a sample (described, for example, at page 29, line 4 – 11) containing target nucleic acid (described, for example, at page 11, lines 4 – 23) from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure (described, for example, at page 25, lines 25 - 30), are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions (described, for example, at Figure 4 "Allele Panel", and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers") selected from the group consisting of *BChE* (described, for example, at page 6, lines 21 – 22), *CYP2D6* (described, for example, at page 6, lines 22 – 24), *F5*

(described, for example, at page 6, lines 28 – 29), *F2* (described, for example, at page 6, line 2), *CACNAIS* (described, for example, at page 7, lines 1 – 2), *MTHFR* (described, for example, at page 6, line 26), *MTR* (described, for example, at page 6, lines 26 – 27), *CBS* (described, for example, at page 6 lines 27 – 28), *TNFα* (described, for example, at page 7, lines 3 – 4), and *TNFβ* (described, for example, at page 7, line 4) (and described, for example, in Figure 5 "Detection of Allelic Variants") to generate a genomic profile (described, for example, at page 3, lines 29 - 30, page 4, lines 7 - 12, page 18, lines 26 - 27, page 5, line 20, page 6, lines 15 - 20, page 8, lines 1 - 2, and lines 10 - 11, page 27, lines 13 – 17, and Figure 5) for use in selecting a perioperative course of action for said subject (described, for example, at page 3, line 30 – page 4, line 2, page 28, lines 9 – 13 and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers"), and thereby providing a subject-specific clinical pathway for said subject (described for example in Figure 1 "Alter Intervention" and Figure 3 "Therapeutic Plan"), comprising information to optimize perioperative care that, based at least on the presence or absence of are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions (described, for example, at Figure 4 "Allele Panel", and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers") selected from the group consisting of *BChE* (described, for example, at page 6, lines 21 – 22), *CYP2D6* (described, for example, at page 6, lines 22 – 24), *F5* (described, for example, at page 6, lines 28 – 29), *F2* (described, for example, at page 6, line 2), *CACNAIS* (described, for example, at page 7, lines 1 – 2), *MTHFR* (described, for example, at page 6, line 26), *MTR* (described, for example, at page 6, lines 26 – 27), *CBS* (described, for example, at page 6 lines 27 – 28), *TNFα* (described, for example, at page 7, lines 3 – 4), and *TNFβ* (described, for example, at page 7, line 4) (and described, for example, in Figure 5 "Detection of Allelic Variants") directs a user (described, for example, in Figure 1 "MD User Interpretation" and at page 10, lines 17 – 20, page 50, lines 8 – 18, page 50, line 19 – page 53, line 3, and page 35, line 22 – page 40, line 4, "Applications and Interventions for Specific Markers"), to a specific clinical pathway of anesthesia intervention for said subject (described, for example, at page 4, line 24 – page 5, line 3, and page 5, lines 6 – 8).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are two grounds of rejection to be reviewed on appeal:

Ground of Rejection 1 – Whether claims 108-112 are obvious over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, pages 471-476 (hereinafter "Quane") or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "LaDu, 1995") and LaDu (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991 (hereinafter "LaDu, 1991") or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol. 286, pages 487-491, October 1999) (hereinafter "Evans") or Poort *et al.* (Blood, vol 88 No. 10, page 3698-3703, 1996) (hereinafter "Poort") and further in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42047, January, 1999) (hereinafter "Hacia") and further in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) (hereinafter, "Ahern") and Anderson et al. (US Pat 6,267,722, July 31, 2001) (hereinafter "Anderson") as applied to claims 72-107 and further in view of the specification (hereinafter "Specification") (Tables 1-4) .

Ground of Rejection 2 – Whether claims 72-107 are obvious over Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "LaDu, 1995") and LaDu (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991 (hereinafter "LaDu, 1991") and Pharmacogenetics (Chapter 4, pages 309-326) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol. 286, pages 487-491, October 1999) (hereinafter "Evans") in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42047, January, 1999) (hereinafter "Hacia") and further in view of Ahern (The Scientist, Vol 9, No. 15, page 20, July 1995) (hereinafter, "Ahern") and Anderson et al. (US Pat 6,267,722, July 31, 2001) (hereinafter "Anderson").

VII. ARGUMENT

A. Ground of Rejection 1 – Whether claims 108-112 are obvious over Miller in view of Quane or LaDu, 1995 and LaDu, 1991 or Pharmacogenetics and Evans or Poort and further in view of Hoon and Hacia and further in view of Ahern and Anderson as applied to claims 72-107 and further in view of the specification (Tables 1-4).

The factual inquiries set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 35 U.S.C. are summarized as follows:

1. Determining the scope and contents of the prior art
2. Ascertaining differences between the prior art and the claims at issue
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The test for *prima facie* obviousness is consistent with legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). The Federal Circuit summarized the Supreme Court's holding in *KSR* that "While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test, the Court acknowledged the importance of identifying "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus., Ltd. v. Alphapharma Pty., Ltd., 06-1329, slip op. (Fed. Cir. June 28, 2007)*, at 13-14 (quoting *KSR,* 127 S. Ct. at 1731) (emphasis added). Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR,* 127 S. Ct. at 1731. The *KSR* Court upheld the secondary considerations of non-obviounsess, noting that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143.

The Appellant submits that the Office has failed to establish a prima facie case of obviousness because: 1) the Office has erred in determining the scope and contents of the prior art and in ascertaining differences between the prior art and the claims at issue;

2) the cited references do not teach or suggest all elements of the presently claimed invention; and 3) the Office has not provided a motivation to combine the references.

1. The Office has erred in not properly determining the scope and contents of the prior art, and in ascertaining differences between the prior art and the presently claimed invention

In the Final Office Action of March 24, 2008 the Office concedes:

> "Miller, Quane, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia do not specifically teach profiling of each of BchE, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, CTP2 (sic), TNFA and TNFB.
> The instant specification teaches markers in each of these genes which are associated with various operative related disorders. The specification clearly illustrates genes and mutations which are associated with particular mutations. The response filed March 26, 2001 specifically illustrates that the invention does not claim discovery of newly identified sequences (page 7).
> Therefore, it would have been obvious in view of the teachings of Miller, Quane, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia to include any number of genes on the array of Hacia for the high throughput analysis of operatives (sic) complications.
> **Response to Arguments**
> The response traverses the rejection. The response asserts the rejection fails to teach all of the limitations for the reasons discussed above. This argument has been considered but is not convincing for the reasons provided above. Thus for the reasons above and those already of record, the rejection is maintained." (Final Office Action of March 24, 2008, pages 19-20.)

The Appellant submits that the Office has failed to establish a prima facie case of obviousness because the Office has erred in determining the scope and contents of the prior art, and in ascertaining differences between the prior art and the claims at issue. For example, contrary to the Office's characterization, claims 108-112 do not teach or

suggest reagents sufficient to detect the presence or absence of variant alleles in *RYR1*. None of the cited Also, in the Final Office Action of March 24, 2008 the Office does not express the relevance of the Quane reference to the kits of the presently claimed invention.

As well, the Final Office Action of March 24, 2008 the Office fails to express the relevance of the Miller reference to the kits of the presently claimed invention.

In turn, the filing date of the presently claimed invention is October 12, 2001. The Appellant submits that the Final Office Action of March 24, 2008 fails to provide the origin of "the response filed March 26, 2001". Clearly, "the invention" of the earlier filed response, and the kits of the presently claimed invention are different. The Office nevertheless fails to express this difference, or to express the relevance of "the response filed March 26, 2001" to the kits of the presently claimed invention.

In addition, the Appellant submits that in the Final Office Action of March 24, 2008 the Office has erred in determining the scope and contents of the alleged prior art. For example, the Office notes:

> "Specifically, codeine should be administered with care to individuals having certain BchE mutations." (Final Office Action of March 24, 2008, page 8.)
>
> And:
>
> "Therefore, the skilled artisan would have additionally analyzed a patient for . . . venous thromboembolism, as taught by Acta Anaesthesiologica Scandinavica, LaDu, Pharmacogenetics, or Evans." (Final Office Action of March 24, 2008, page 7.)

To the contrary, the Appellant notes that codeine is metabolized by CYP2D6 not BChE, and that Acta Anaesthesiologica Scandinavica, LaDu, Pharmacogenetics, or Evans, alone or in combination, do not teach or suggest kits for detection of alleles causing venous thromboembolism. Thus, the rejection is based on factually incorrect assumptions.

Moreover, the Appellant submits that the present claims are not drawn to "any number of genes" in view of the teachings of Miller, Quane, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia as the Office suggests. Rather, claims 108-112 are drawn to the detection of variant alleles in a specific grouping of genes *i.e.*, *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β, pointing to the Office's failure to properly determine the scope and contents of the prior art, and failure to properly ascertain differences between the prior art and the kits of claims 108-112.

2. The cited references do not teach all elements of the presently claimed invention

The Appellant submits that the Office's combination of references fails to teach all elements of the claims. For example, none of the Office's cited alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding factor 5 (*F5*). None of the Office's cited alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding the alpha subunit of the skeletal muscle voltage dependent calcium channel (*CACNAIS*). None of the Office's cited alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding methionine synthase (*MTR*). None of the Office's cited alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding methionine synthase reductase (*MTRR*). None of the Office's alleged prior art references, alone or in combination, teach or suggest reagents sufficient to detect the presence or absence of variant alleles in the gene encoding cystathionine beta-synthase (*CBS*).

As well, none of the Office's references, alone or in combination, teach or suggest the element of reagents that are sufficient to detect the presence or absence of variant alleles **in each of** *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β (*i.e.*, none provide the claimed combination). The Appellant submits

that the Final Office Action of March 24, 2008 fails to examine, or even recognize, this element of claims 108-112.

Moreover, the Appellant submits that the Office's combination of references fails to teach or suggest all elements of the independent claims upon which claims 108-112 depend. For example, in the Final Office Action of March 24, 2008 the Office is explicit in its reason for providing Anderson:

> "Although the examiner believes In re Ngai specifically speaks to this issue, in an effort to provide that computers for obtaining data, synthesizing the data and then outputting information for risk index were known at the time the invention was made, Anderson was made of record in the instant application." (Final Office Action of March 24, 2008, page 10.)

The Appellant submits that although the Office is explicit in its reason for providing Anderson, it fails to remedy the missing elements of the Office's combination of references. For example, a missing element in the Office's combination of references is not a generic computer for obtaining data, synthesizing the data and then outputting information. Rather, a missing element in the Office's combination of references is a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents in the kits of the presently claimed invention *i.e.*, reagents that are sufficient to detect the presence or absence of variant alleles **in each of** *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β. The Appellant submits that the Final Office Action of March 24, 2008 fails to indicate where in the Office's combination of references, these missing elements are to be found.

3. There is no motivation to combine the references in the manner indicated by the Office

The Appellant submits that in the Final Office Action of March 24, 2008 the Office has failed to provide a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements, *i.e.*, reagents that are sufficient to detect the presence or absence of variant alleles in each of *BChE, CYP2D6, F5, F2, CACNAIS,*

MTHFR, MTR, MTRR, CBS, TNFα and *TNFβ*, in the way the claimed new invention does *i.e.*, the kits of claims 108-112. For example, the Office fails to express why an artisan of ordinary skill would have been motivated to combine the teachings of Miller, Quane, AAS, LaDu, Pharmacogenetics, Poort, Hoon and Hacia with Anderson to arrive at the kits of the presently claimed invention. Only through improper hindsight has the Office pieced together disparate references to compile the claimed set of markers (although, as noted above, these references do not actually describe each of the markers in the claimed set). No proper motivation has been provided to explain why the specific set of claimed markers would be assembled for analysis as opposed to the innumerable number of other possible combinations of markers in the literature. Clearly, Anderson does not teach or suggest the kits of the presently claimed invention, or a kit of any kind. As well, Anderson does not teach or suggest instructions on a computer medium for use with a kit. Accordingly, in the Final Office Action of March 24, 2008 there is no explicit or implicit teaching or suggestion or motivation why an artisan of ordinary skill would turn to Anderson to generate the kits of claims 108-112.

4. Conclusion

In view of the points of non-obviousness discussed above, it is clear that the Office's combination of Miller, Quane, LaDu, 1995, LaDu, 1991, Pharmacogenetics, Evans, Poort, Hoon, Hacia, Ahern and Anderson does not provide a prima facie case of obviousness of claims 108-112.

B. Ground of Rejection 2 - Whether claims 72-107 are obvious over LaDu, 1995 and LaDu, 1991, and Pharmacogenetics and Evans, in view of Hoon and Hacia, and further in view of Ahern and Anderson.

The Appellant submits that the Office has failed to establish a prima facie case of obviousness because: 1) the cited references do not teach all elements of the presently claimed invention; 2) the Office has not provided a motivation to combine the references; and 3) the Office has erred in determining the scope and contents of the prior art and in ascertaining differences between the prior art and the claims at issue.

1. The cited references do not teach all elements of the presently claimed invention

The Appellant submits that the Office's combination of references fails to teach all elements of the claims. For example, none of the Examiner's references, alone or in combination, teach or suggest a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents. For example, in the Final Office Action of March 24, 2008 the Office notes:

> "Further, with regard to the limitation that the kits contain instructions for using said kit for generating said perioperative genomic profile for said subject, the inclusion of instructions is not considered to provide a patentable limitation on the claims. See In re Ngai, 367 F. 2d 1336, 70 U.S.P.Q. 2d 1862 (Fed. Cir. 2004). (holding that an inventor could not patent known kits by simply attaching [a] new set of instructions to that product)." (Office Action of March 24, 2008, page 2.)

In its prior Decision on Appeal mailed July 31, 2006, the Board of Patent Appeals and Interferences expressly considered this element of claim 72:

> "Finally, the kit defined by claim 72 comprises "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents."" (Decision on Appeal mailed July 31, 2006, page 5). (Emphasis added.)

> Accordingly, the Board of Patent Appeals and Interferences concluded:

> "In our view, these disclosures (*i.e.*, of the Specification) reasonably support the concept of combining reagents for detecting variant alleles with a computer program to analyze data indicating the presence or absence of such variant alleles." (Decision on Appeal mailed July 31, 2006, page 8). (Emphasis added.)

> And:

> "However, on page 4 of the Examiner's Answer, the examiner quotes the following passage from the specification: "In some embodiments, a computer based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician)e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of disease) (emphasis added). While this passage does not use precisely the same words as claim 72, we agree with Appellant that it reasonably describes **the limitation recited in the claim**. (Decision on Appeal mailed July 31, 2006, page 6). (Underlining in original, bold emphasis added.)

In the Final Office Action of March 24, 2008 the Office improperly dismisses this limitation of the claims that has previously been expressly recognized and accepted by the Board of Appeals and Interferences. In this assertion the Office has made a number of errors.

First, the Board of Appeals and Interferences has already considered the Office's arguments with regard to *In re Ngai* (See, for example, Examiner's Answer mailed December 30, 2005, pages 18-22), and has found the Office's assertions non-persuasive. The Office is bound by the Board's decision. Surprisingly, in the Office Action of March 24, 2008 the Office notes "there is no indication of the Board's position on this matter or record." (Office Action of March 24, 2008, page 10)

Second, at the time of its Decision the Board of Patent Appeals and Interferences was in possession of a detailed consideration of *In re Ngai* in the Appellant's Reply Brief filed by the Appellant on March 3, 2006. In its Decision on Appeal of mailed July 31, 2006, the Board of Patent Appeals and Interferences does not rebut a single point or issue raised by the Appellant with regard to the inapplicability of *In re Ngai* to the prosecution of the present application.

Third, the kits of the claimed invention are not "known kits". This point was brought to the Office's attention in the Amendment and Response to Office Action Dated

September 12, 2006, page 12, and in the Response to Office Action Dated June 18, 2007, page 12. In Final Office Action of March 24, 2008 the Office notes:

> "This argument has been reviewed but is not convincing, because in light of the teachings in the art, the kits would have been obvious." (Final Office Action of March 24, 2008, page 10.)

The Appellant submits that the Office has never indicated where such "known kits" are to be found, other than in the present application. Accordingly, *In re Ngai*, wherein an applicant is precluded from substituting one set of instructions for another with the same previously disclosed product, is irrelevant to the presently claimed invention wherein such kits were clearly unknown at the time the invention was made.

Fourth, the Office has never indicated where in the Office's references, either alone or in combination, such kits (*e.g.*, kits with "reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β so as to generate a genomic profile for use in selecting a perioperative course of action for said subject") are to be found. In the Final Office Action of March 24, 2008 the Office notes:

> "Fourth, the response asserts the Examiner has not indicated where kits are to be found. This argument has been reviewed but is not convincing. Kits are routine in the art for simplicity. The examiner specifically included the Ahern reference to address applicants concerns that kits were not known at the time the invention was made." (Final Office Action of March 24, 2008, pages 10-11.)

The Appellant notes that whether or not the kits of the presently claimed invention are to be found in the Office's combination of references is at issue, not the

presence or absence of kits as a generic concept in the art. The Appellant submits that kits of the presently claimed invention are clearly not to be found in the Office's combination of references. Ahern teaches kits for, for example: expression of proteins from cloned genes; for labeling DNA or RNA probes with radioisotopes or fluorescent tags; for labeling oligonucleotides by conjugation with alkaline phosphatase; for small-scale purifications; for isolating cells from whole blood for cytotoxicity assays; for painting chromosomes with fluorescent dyes; for cryopreserving mouse embryos; and for signal transduction research.

Ahern does not teach or suggest kits sufficient to detect variation in one gene. Ahern does not teach or suggest kits sufficient to detect variation in two genes. Ahern does not teach or suggest kits sufficient to detect variation in two or more genes selected from a group of genes, or in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNA1S, MTHFR, MTR, MTRR, CB, TNFα and TNFβ.* These missing elements were pointed out to the Office in the Response to Office Action Dated June 18, 2007, page 15. In the Final Office Action of March 24, 2008 the Office is unresponsive to these facts. Indeed, to the extent that Ahern contemplates characterization of DNA, Ahern discourages use of such kits:

> "Some tasks … such as constructing genomic libraries, designing primer sets for sequencing, or synthesizing nucleic acids or peptides … are so daunting that for many scientists it makes more sense to hire out." (Ahern, page 5).

In the Final Office Action of March 24, 2008 the Office misconstrue's Ahern's simple and unambiguous statement:

> "This specifically illustrates that companies can make kits with reagents desirable to those scientists seeking to characterize DNA, for example." (Final Office Action of March 24, 2008, page 12.

To the contrary, the Appellant submits that Ahern clearly directs scientists away from kits for this purpose, directing scientists instead to hire others for DNA characterization.

Fifth, the Office confuses the printed matter instructions of *In re Ngai* with a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents of the claims. As pointed out to the Office (Response to Office Action Dated June 18, 2007, page 13), computer instructions which direct a processor to analyze data for generating a perioperative genomic profile for a subject as claimed, qualify as statutory subject matter because storage of the computer instructions turns a computer readable medium into a functional component which directly cooperates with the processor. Computer instructions cause computer functions to occur, and are therefore inarguably functional components of the computer system. These facts have been acknowledged by the Board of Appeals and Interferences, and are uncontested in the Final Office Action March 24, 2008.

To the contrary, in the Final Office Action of March 24, 2008 the Office notes:

> "The response suggests that the references did not teach or suggest a computer program comprising instruction which direct a processor to analyze data derived from said reagents. Although the examiner believes In re Ngai specifically speaks to this issue, in an effort to provide that computers for obtaining data, synthesizing the data and the outputting information for risk index were well known at the time the invention was made, Anderson was made of record in the instant application." (Final Office Action of March 24, 2008, page 10.)

> And:

> "Applicant's fifth argument is directed to the printed matter of In re Ngai vs. the computer program comprising instructions directing a processor to analyze data derived from such reagents. This argument has been reviewed but is not persuasive. The instructions as intended use in the kit of Ngai and the instructions on a computer program as intended use in the instant applications are analogous. Applicant appears to be attempting to place instructions in a different format, i.e.

> a computer to frustrate the intent of Ngai." (Final Office Action of March 24, 2008, page 11.)
>
> And:
>
> "As noted above, the information provided in the form of instructions in a kit does not carry patentable weight, as held in Ngai." (Final Office Action of March 24, 2008, pages 11-12.)

The Appellant submits that the Board has previously recognized that the computer programs of the presently claimed invention are patentable subject matter. Accordingly, the computer programs of the presently claimed invention are clearly not analogous to Ngai's "instructions of intended use", or the Office's "instructions on a computer program as intended use". Nor do the computer programs of the presently claimed invention "frustrate the intent of Ngai". As pointed out to the Office:

> "Contrary to the Examiner's misinterpretation, *In re Ngai* does not address, consider or even mention computers, computer programs, computer programs comprising instructions, or computer analysis of data." (Response to Office Action Dated June 18, 2007, page 13) (Emphasis in original).

In turn, the Appellant submits that the Office's addition of Anderson does not remedy the multiple defects of the Office's combination of 7 other references. For example, Anderson does not teach or suggest a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, the subject being a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR,*

MTRR, CBS, TNFα and *TNFβ* so as to generate a genomic profile for use in selecting a perioperative course of action for said subject.

For at least these reasons, and as accepted by the Board of Appeals and Interferences, "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents" (*i.e.*, not merely any computer program that the Office is able to locate in the alleged prior art) is a proper and statutory element of claims 72-105. None of the Office's references, alone or in combination, teach or suggest this element. In turn, none of the Office's references, alone or in combination, teach or suggest the limitation "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents to indicate an anesthesia treatment course of action." (Independent claim 84.) As well, none of the Office's references, alone or in combination, teach or suggest the limitation "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents to indicate a surgical treatment course of action." (Independent claim 101.) These missing elements were pointed out to the Office in the Response to Office Action Dated June 18, 2007 pages 13-14. The Office Action of March 24, 2008 is unresponsive to these facts.

As well, in the Final Office Action of March 24, 2008 the Office fails to address elements of dependent claims that are missing from the Office's combination of references. For example, in order to establish prima facie obviousness, the Office must point to a reference, or combination of references, that teaches or suggests a computer program with software that analyzes data from the kit of the claimed invention, and generates, for example, recommendations for treatment options based on the presence or absence of variant alleles in *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ*. The Office has never identified such a computer program in the cited references taken alone, or in combination. Nowhere in the Office's cited references is knowledge of variant alleles in two or more genes selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ* combined to indicate an anesthesia treatment course of action (claim 84), a surgical treatment course of action (claim 101), a specific clinical pathway of medical intervention (claim 106), or a specific clinical pathway or anesthesia intervention (claim

107). None of the Office's references teach or suggest how to perform, or even whether to perform, the combination of data from the claimed variant alleles, and translation of this data into a subject-specific treatment course of action. These missing elements were pointed out to the Office in the Response to Office Action Dated June 18, 2007 page 14. The Office Action of March 24, 2008 is unresponsive to these facts.

Nor do the Office's cited references teach or suggest a computer program that directs the fate of the genetic data according to the subject's preference (claim 82), or that directs a user to a specific perioperative clinical pathway for a subject (claim 83). None of the rejection's references teach or suggest kits with reagents sufficient to detect variant alleles in *F5, F2, CACNA1S, MTR, MTRR,* and *CBS.* What is missing from the Office's references is a disclosure of, for example, primers and probes specific to these genes and these alleles. None of the Office's references, alone or in combination, teach or suggest kits sufficient to detect the presence or absence of variant alleles in two or more genes, or even kits sufficient to detect of the presence or absence of variant alleles in a single gene. These missing elements were pointed out to the Office in the Response to Office Action Dated June 18, 2007 pages 14-15. The Office Action of March 24, 2008 is unresponsive to these facts.

Because the Office's references individually, and in combination, fail to teach all elements of claims 72-105, and indeed teach away from one another, the Appellant submits that the Office has failed to establish the *prima facie* obviousness of the claims.

2. There is no motivation to combine the references in the manner indicated by the Office

The Supreme Court in *Graham* established specific steps for a non-obvious analysis: (1) determine the scope and content of the prior art; (2) evaluate the differences between the prior art and the claims at issue; and (3) determine the level of ordinary skill in the art.[1] "Against this background, the obviousness or non-obviousness of the subject matter is determined."[2] These *Graham* steps provide a subjective analysis of whether an invention was obvious at the time it was made. Objective evidence, termed "secondary

[1] See *Graham*, 383 U.S. at 17.
[2] Id.

consideration" evidence, that an invention was not obvious at the time it was made also may be introduced.[3] Such secondary consideration evidence could include, for instance, the commercial success of an invention or that the invention filled a long-felt need. The Supreme Court recognized the use of secondary consideration evidence in *Graham* in an effort to "guard against slipping into use of hindsight."[4] The Federal Circuit has followed this holding and ruled that it is "error to exclude [secondary consideration] evidence from consideration."[5] In an effort to achieve this goal, courts have recognized a variety of types of secondary consideration evidence, including: long-felt need,[6] commercial success,[7] the failure of others to achieve the invention,[8] licensing by others,[9] and unexpected results or advantages.[10]

Thus, the non-obvious standard of §103(a) requires the Examiner to make a historical judgment: whether the invention would have been obvious at the time the invention was made in the past. To reach a proper non-obvious conclusion, the Office must not only step backward in time to a moment when the invention was unknown, but also avoid letting knowledge that the invention was achieved affect the Office's decision about whether it was obvious at the time it was achieved.[11] The courts have recognized that meeting this standard "requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."[12]

In an effort to preclude such an improper result, the Federal Circuit requires that the non-obvious analysis be conducted viewing the invention as a whole.[13] Using

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[3] *Id.* at 17-18.
[4] *Id.* at 36 (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co.*,332 F.2d 406, 412 (1964)).
[5] *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983).
[6] *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000)
[7] *Id.* at 1377-1378.
[8] *Id.* at 1378-1379.
[9] *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed.Cir. 2000).
[10] *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1382–83 (Fed.Cir. 1986).
[11] *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966)
[12] *In re Dembiczak*, 175 F.3d at 999 (emphasis added); see also *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983) ("It is difficult but necessary that the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.").
[13] See *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004).

'"hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention"'[14] or conducting a "reference-by-reference, limitation-by-limitation analysis" fails to demonstrate how the invention is obvious in light of prior art.[15] Similarly, the Examiner may not use the invention as a blueprint for linking together pieces of prior art in order to find the invention obvious.[16] The Federal Circuit has referred to using the invention as a "blueprint for piecing together the prior art . . . [as] the essence of hindsight."[17]

The Appellant submits that the Office has clearly and improperly utilized hindsight reconstruction of the claimed invention in an effort to support the allegation that the claimed invention is prima facie obvious. The Appellant contends that, at the time the invention was made, there existed no explicit or implicit teaching or suggestion or motivation to combine elements present in the art to generate the presently claimed invention. Prior to the disclosure of the present invention, there existed no teaching, from anywhere, regarding the kits and computer programs of the presently claimed invention.

The Appellant submits that the Office has inappropriately utilized the disclosure of the invention in an attempt to recreate the invention. In the Office Action of March 24, 2008 the Office argues:

> "The ordinary artisan would have been motivated to have packaged reagents needed to screen individuals to determine the genetic composition of the individuals to provide individualized diagnosis and to avoid any fatal reaction to the anesthesia in a quick and efficient cost effective kit." (Final Office Action of March 24, 2008, page 7).
>
> And:

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[14] *Ecolochem, Inc. v. S. Cal. Edison Co*., 227 F.3d 1361, 1371 (Fed. Cir. 2000) (quoting *In re Fine*, 837 F.2d 1071, 1075 (1988)).
[15] *Id*., at 1374
[16] *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).
[17] *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)

> "Thus, the ordinary artisan would have been motivated to have packaged the primers, probes, and reagents of Acta Anaesthesiologica Scandinavica, LaDu, Pharmacogenetics, or Evans and Hacia and Hoon which are necessary for determining the genotypes of BchE and CYP2D6 which are associated [with] poor reactions to anesthesia into a kit, as taught by Ahern for the express purpose of saving time and money and included a computer program taught by Anderson for the digitization, integraton and convenience of patient information, and risk index." (Final Office Action of March 24, 200, page 8).

At multiple points in the Final Office Action of March 24, 2008 the Office acknowledges the advantages of the presently claimed invention, and identifies one of ordinary skill in the art as a clinician. Moreover, the Office expressly recognizes an anesthesiologist as one of ordinary skill in the art:

> "The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether plausible substitutes may be provided to patients which would not cause these conditions to arise." (Final Office Action of March 24, 2008, pages 7-8.) (Emphasis added.)

> And:

> "Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patient's genetic make-up." (Final Office Action of March 24, 2008, page 8.) (Emphasis added.)

Accordingly, the Applicant submits that the Examiner's speculations and conclusory statements regarding the motivation and common sense of the ordinary artisan

anesthesiologist to combine the claim elements to yield the claimed invention are unsupported by proper evidence and are in error.

In the Response to Office Dated June 18, 2007 the Appellant submitted the Declaration of Dr. Kirk Hogan. In his Declaration Dr. Hogan (Declaration of Kirk Hogan M.D. Under 37 C.F.R. 1.132, pages 2-3.) explains that prior to the perioperative genomic profile kits of the presently claimed invention, anesthesiologists of ordinary skill were not aware of, and did not use, kits for genomic analysis of single or multiple polymorphisms, genes or diseases. Dr. Hogan explains that:

> "5. For many decades before the perioperative genomic profile kits of the present patent application, anesthesiologists were highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations. Nevertheless, anesthesiologists did not arrive at the kits of the presently claimed invention."

In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "6. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of single polymorphisms, single genes or single diseases."

In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "7. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of single polymorphisms, single genes or single diseases.

In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "8. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases."

In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "9. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases."

In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts let alone provide contrary evidence.

Dr. Hogan also explains that:

> "10. While the anesthesiologist of ordinary skill has for many decades recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery, anesthesiologists of ordinary skill could not have combined the claimed elements because they lacked the requisite appreciation of the technical knowledge to arrive at the perioperative genomic profile kits of the presently claimed invention as a solution to the problems addressed by the presently claimed invention."

In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts let alone provide contrary evidence.

To the contrary, in the Final Office Action of March 24, 2008 the Office responds:

> "Here the declaration <u>does not appear to provide any evidence</u>." (Final Office Action of March 24, 2008, page 14.) (Emphasis added.)

And:

> "The declaration appears to be focusing on the fact that anesthesiologists did not arrive at the kits. However, the standard required is that one of skill in the art. One skilled in the art would encompass molecular biologists who were performing association studies between polymorphisms an poor reactions to anesthesiology." (Final Office Action of March 24, 2008, page 14.)

The Appellant submits that in these conclusions the Office has made a number of errors. First, the proper standard is one of ordinary skill in the art, not one of exceptional skill *i.e.*, a researcher or an author of an academic manuscript. Second, elsewhere in the Final Office Action of March 24, 2008 the Office clearly establishes an anesthesiologist as an artisan of ordinary skill for the purposes of performing an obviousness analysis. (See Final Office Action of March 24, 2008, pages 7-8.) It is improper to switch the identity of the skilled artisan to support an argument when convenient (*i.e.*, when but for the switch the argument would fail). This is a fundamental error in the rejction.

Third, even if a molecular biologist could be considered an artisan of ordinary skill, and the Appellant submits that one could not, the Office provides no evidence that such a molecular biologist would have been motivated to make the Office's combination and thereby arrive at the claims of the present invention. For example, the Office has made no showing that a molecular biologist of ordinary skill would have been motivated to combine reagents configured to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ* with a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents. Indeed, this is contrary to the art and the evidence in the record. Molecular biologists of ordinary skill did not and would not assemble the clinically relevant claimed markers or provide software to analyze them.

To the contrary, the Appellant submits that Dr. Hogan's Declaration provides clear-cut, expert, and uncontested evidence that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations "for many decades", and that

despite this motivation artisans of ordinary skill of any background failed to achieve the presently claimed invention at the time the invention was made.

In the Response to Office Dated June 18, 2007 the Appellant submitted the Declaration of Dr. Douglas Baird Coursin. In his Declaration, Dr. Coursin explains that there was no suggestion or teaching in the prior art for periperative genomic profiles. Dr. Coursin further explains the long felt and unmet need for this solution to the problem of inborn predispositions to complications during anesthesia and surgery, and the unexpected success of the technology. Dr. Coursin is one of the leading anesthesiologists in the country, and has been for many years. Dr. Coursin explains that skilled artisans, such as anesthesiologists, have as a primary mission to solve the problem solved by the present invention. Yet even with this long-felt need and years of searching by innumerable practitioners, no one solved this long-felt need using the approach of the present invention. In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts.

In a situation like the present one, there may be no better evidence of non-obviousness than the failure of an entire field to solve their primary problem, even with a wealth of information and technology known in the literature. As Dr. Coursin notes:

> "However, if the perioperative genomic profiles of the present patent application were obvious, the ordinary practitioner would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. No person having ordinary skill in the art, or even extraordinary skill, took this step before the claimed invention was made." (Declaration of Douglas Baird Coursin, M.D. Under 37 C.F.R. 1.132, page 3.)

In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts. The field failed to realize the solution because the solution was not obvious to these skilled artisans. These skilled artisans would not, and did not, see the combination the Office proposes that they should have and would have seen.

In the Final Office Action of March 24, 2008 the Office responds:

> "Similar to the declaration provided by Dr. Hogan, the declaration under 37 C.F.R. 1.132 filed December 18, 2007 is insufficient to overcome the rejection of claims as set forth in the last office action because: It states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. (Final Office Action of March 24, 2008, page 14.)

To the contrary, the Appellant submits that Dr. Coursin's Declaration provides clear-cut, expert, and uncontested evidence that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations for 26 years "and well before". Dr. Coursin's Declaration provides evidence that the need was persistent and recognized by those of ordinary skill in the art.

The Appellant submits that the Office's rejection is based on hindsight knowledge of the invention wherein the Office has assumed what skilled artisans *should have* thought of the invention in view of numerous disparate pieces of prior art. In making the rejection, the Office (*i.e.*, not one of skill in the art, and who is in possession of hindsight knowledge of the invention), has *seen* an invention that the entire world of skilled artisans, focused for many years on the exact problem solved by the invention, had failed to see. Artisans, of ordinary and extraordinary skill in the field, who have devoted their careers to solving this problem, failed to put together the Office's combination of references, and failed to solve the problem. The only logical explanation is that the invention is non-obvious. In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts.

Notably missing from the Office's rejection is placement in the hands and minds of the appropriate skilled artisans of: 1) the prior art of record (is this the type of work one skilled in the art would have reviewed in assessing the problem?); and 2) the mental and experimental process for modifying the art to arrive at the invention (even if they would have reviewed the cited art, would they have put the pieces together and modified the pieces appropriately?). At no point in the Final Office Action of March 24, 2008 does

the Office provide evidence of the handling of the references in the hands and minds of the appropriate skilled artisan. Regardless, even if the Office had done this, the evidence of long-felt but unresolved need demonstrates that skilled artisan did not, and would not, arrive at the invention. If it were obvious, they would have done it years before the filing of the present application. In the Final Office Action of March 24, 2008 the Office does not contest or even address these facts.

The Supreme Court specifically states:

> "Often it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit." (*KSR Int'l Co. v. Teleflex, In.,* 550 U.S., 127 S. Ct. 1727 (2007).) (Emphasis added.)

The Appellant asserts that in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of 8 prior art elements (*vs.* 2 prior art references in *KSR v. Teleflex*), the Office has clearly failed to identify the reason why a person of ordinary skill in the art would have made the combination in the manner claimed. In making such a reconstruction, the Office may only take into account the common knowledge which was within the level of ordinary skill at the time the claimed invention was made, and may not include, as here, knowledge gleaned only from the Appellant's disclosure or unsupported assumptions about the mindset of the skilled artisan. (See *In re McLaughlin*, 443 F/2d 1392, 170 USPQ 209 CCPA, 1971.) The determination of whether a combination is a predictable variation of the prior art must be evaluated from the perspective of the person of ordinary skill in the art at the time claimed invention was made. Dr. Hogan's and Dr. Coursin's Declarations provide material evidence that Office's speculations regarding the level of ordinary skill are in clear error.

In the Final Office Action of March 24, 2008 the Office notes:

"Finally, Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come prepared." (Office Action of June 18, 2007, page 5)

In relying upon these arguments to support a prima facie case of obviousness, the Office has made a number of errors. First, The Office's acknowledgment of the benefits of the claimed invention made after the Office was in possession of the specification and claims does not, and cannot, substitute for substantial evidence of what an artisan of ordinary skill would or would not have been motivated to do at the time the invention was made. To the contrary, the in the Final Office Action of March 24, 2008 the Office improperly persists in asserting new standards of the ordinary artisan's motivation to combine references *i.e.*, to "save time and money", and "to avoid any fatal reaction." In *In re Sang Su Lee* the Court of Appeals for the Federal Circuit expressly prohibits this kind of substitution of the benefits of an invention for objective evidence of an invention's obviousness by the Office.[18] On multiple occasions in the prosecution of the present application the Examiner has had the opportunity to address this holding, and has never done so.

The Appellant submits that the Office's improper combination of references, and failure to respond to numerous facts in the Appellants Response to the Office Action Dated June 18, 2007, preclude a finding of prima facie obviousness of the claims.

3. The Office has erred in not properly determining the scope and contents of the prior art, and in ascertaining differences between the prior art and present claims 106 and 107

In the Final Office Action of March 24, 2008 the Office notes:

"The response further asserts that the rejection fails to address the content of the kits instructions as provided in claims 82-84, 101, 106 and 107, for example." (Final Office Action of March 24, 2008, page 11.)

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[18] *In Re Sang Su Lee*, 277 F.3d 1338, 1341, USPQ2d 1430, 1433. (Fed. Cir. 2002).

The Appellant submits that the Office has failed to determine the scope and contents of the presently claimed invention. For example, claims 106 and 107 do not teach or suggest "kit instructions" as characterized by the Office. In the Final Office Action of March 24, 2008 the Office fails to examine, or even address, the patentability of claims 106 and 107 as recited. Missing elements in claims 106 and 107 were pointed out to the Office in the Response to Office Action Dated June 18, 2007, pages 16 and 17. The Final Office Action of March 24, 2008 is unresponsive to these facts. Because the Office's references individually, and in combination, fail to teach or suggest all elements of claims 106-107, the Office has failed to establish prima facie obviousness of the claims.

4. Conclusion

In view of the points of non-obviousness discussed above, it is clear that the Office's combination of LaDu, 1995, LaDu, 1991, Pharmacogenetics, Evans, Hoon, Hacia, Ahern and Anderson does not provide a prima facie case of obviousness of claims 108-112.

C. Conclusion

For the foregoing reasons, it is submitted that the Office's rejection of claims 71-112 was erroneous, and reversal of the rejections is respectfully requested. The Appellant requests either that the Board render a decision as to the allowability of the claims, or alternatively, that the application be remanded for reconsideration by the Office.

VIII. CLAIMS APPENDIX

1 - 71 (cancelled).

72. (previously presented) A kit for generating a perioperative genomic profile for a subject, comprising:

a) reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β so as to generate a genomic profile for use in selecting a perioperative course of action for said subject; and

b) a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents.

73. (previously presented) The kit of claim 72, wherein said instructions translate said data into information of predictive value for a clinician.

74. (previously presented) The kit of claim 72, wherein said instructions translate said data into a risk assessment for treatment options.

75. (previously presented) The kit of claim 72, wherein said instructions translate said data into recommendations for treatment options.

76. (previously presented) The kit of claim 72, wherein said instructions generate a report for display to a clinician.

77. (previously presented) The kit of claim 76, wherein said display is in the form of a report that can be printed.

78. (previously presented) The kit of claim 76, wherein said display is in the form of a report on a computer monitor.

79. (previously presented) The kit of claim 72, wherein said instructions are sufficient to receive, process and transmit said data to and from said subject, a clinical laboratory and medical personnel.

80. (previously presented) The kit of claim 79, wherein said transmitting of said data uses an electronic communication system.

81. (previously presented) The kit of claim 80, wherein said electronic communication system transmits said data to a distant computer system for processing.

82. (previously presented) The kit of claim 72, wherein said instructions direct the fate of said data according to said subject's preference.

83. (previously presented) The kit of Claim 72, wherein said instructions comprise information to optimize perioperative care that, based on at least the presence of variant alleles of two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β, directs a user to a specific perioperative clinical pathway for said subject.

84. (previously presented) A kit for generating a perioperative genomic profile for a subject, comprising:

a) reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said

surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β so as to generate a genomic profile for use in selecting a perioperative course of action for said subject; and

b) a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents to indicate an anesthesia treatment course of action.

85. (previously presented) The kit of Claim 84, wherein said instructions indicate a general anesthesia treatment course of action.

86. (previously presented) The kit of Claim 85, wherein said general anesthesia is an inhalational treatment course of action.

87. (previously presented) The kit of Claim 85, wherein said general anesthesia is an intravenous treatment course of action.

88. (previously presented) The kit of Claim 85, wherein said general anesthesia is a combined inhalational and intravenous treatment course of action.

89. (previously presented) The kit of Claim 84, wherein said instructions indicate a regional anesthesia treatment course of action.

90. (previously presented) The kit of Claim 84, wherein said instructions indicate a combined regional and general anesthesia treatment course of action.

91. (previously presented) The kit of Claim 84, wherein said instructions indicate an anesthesia treatment course of action during a medical procedure.

92. (previously presented) The kit of Claim 84, wherein said instructions indicate dosages of analgesic compounds.

93. (previously presented) The kit of Claim 84, wherein said instructions indicate increasing the dosage of analgesic compounds metabolized by CYP2D6.

94. (previously presented) The kit of Claim 84, wherein said instructions indicate decreasing the dosage of analgesic compounds metabolized by CYP2D6.

95. (previously presented) The kit of Claim 84, wherein said instructions indicate prophylaxis for thrombosis.

96. (previously presented) The kit of Claim 84, wherein said instructions indicate increasing prophylaxis for thrombosis mediated by variant alleles of *F5, F2, MTHFR, MTR, MTRR,* and *CBS.*

97. (previously presented) The kit of Claim 84, wherein said instructions indicate decreasing prophylaxis for thrombosis mediated by variant alleles of *F5, F2, MTHFR, MTR, MTRR,* and *CBS.*

98. (previously presented) The kit of Claim 84, wherein said instructions indicate monitoring procedures.

99. (previously presented) The kit of Claim 84, wherein said instructions indicate pre-operative phenotypic tests and consultations.

100. (previously presented) The kit of Claim 84, wherein said instructions provide a prognosis after an anesthesia treatment course of action.

101. (previously presented) A kit for generating a perioperative genomic profile for a subject, comprising:

a) reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β so as to generate a genomic profile for use in selecting a perioperative course of action for said subject; and

b) a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents to indicate a surgical treatment course of action.

102. (previously presented) The kit of Claim 101, wherein said instructions indicate a non-invasive surgical treatment course of action.

103. (previously presented) The kit of Claim 101, wherein said instructions indicate an invasive surgical treatment course of action.

104. (previously presented) The kit of Claim 101, wherein said instructions provide a prognosis after a surgical treatment course of action.

105. (previously presented) The kit of Claim 101, wherein said instructions indicate a post-operative treatment course of action.

106. (previously presented) A perioperative genomic profile kit having component parts configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS,*

MTHFR, MTR, MTRR, CBS, TNFα and *TNFβ*, so as to generate a genomic profile for use in selecting a perioperative course of action for said subject and thereby providing a subject-specific clinical pathway for said subject, comprising information to optimize perioperative care that, based at least on the presence or absence of said variant alleles of two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ* measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

107. (previously presented) A perioperative genomic profile kit having component parts configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ*, so as to generate a genomic profile for use in selecting a perioperative course of action for said subject and thereby providing a subject-specific clinical pathway for said subject, comprising information to optimize perioperative care that, based at least on the presence or absence of said variant alleles of two or more genes associated with two or more conditions selected from the group consisting of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ* measured by said kit, directs a user to a specific clinical pathway of anesthesia intervention for said subject.

108. (previously presented) The kit of claim 72, wherein said reagents are sufficient to detect the presence or absence of variant alleles in each of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ.*

109. (previously presented) The kit of claim 84, wherein said reagents are sufficient to detect the presence or absence of variant alleles in each of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα* and *TNFβ.*

110. (previously presented) The kit of 101, wherein said reagents are sufficient to detect the presence or absence of variant alleles in each of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β.

111. (previously presented) The kit of claim 106, wherein said component parts are sufficient to detect the presence or absence of variant alleles in each of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β.

112. (previously presented) The kit of claim 107, wherein said component parts are sufficient to detect the presence or absence of variant alleles in each of *BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNF*α and *TNF*β.

IX. EVIDENCE APPENDIX

PATENT
Attorney Docket No. **HOGAN-04448**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan	
Serial No.:	09/613,887	Group No.: 1634
Filed:	07/11/00	Examiner: J.A.. Goldberg
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**	

DECLARATION OF DOUGLAS BAIRD COURSIN, M.D. UNDER 37 C.F.R. §1.132

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF MAILING UNDER 37 C.F.R. 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.o. Box 1450, Alexandria, VA 22313-1450

Dated: 6-11-07 By: _____
Mary Ellen Waite

Dear Madam:

I, Douglas Baird Coursin, M.D., do hereby declare as follows:

1. I received an M.D. in 1976 from Albany Medical College. I am a Diplomate of the National Board of Medical Examiners, the American Board of Internal Medicine, and the American Board of Anesthesiology with a Special Certificate of Competence in Critical Care Medicine. I am a Professor of Anesthesiology and Internal Medicine at the University of Wisconsin School of Medicine and Public Health. In 1996 – 1997, I served as President of the American Society of Critical Care Anesthesiologists. I've been an elected member of the Board of Directors of the American Board of Anesthesiology since 2001. I presently serve on the editorial boards of Current Opinions in Anaesthesiology, The Mayo Clinic Proceedings, and Critical Care Medicine. I am the 2006 recipient of the American Society of Critical Care Anesthesiologists Lifetime Achievement Award.

2. I understand that methodology for perioperative genomic profiles is disclosed and claimed in the patent application in connection with which this declaration is being submitted. The perioperative genomic profiles of the present patent application represent a completely novel approach that is not obvious in view of existing technologies. To my

knowledge, no one previously proposed or disclosed perioperative genomic profiles that would be successful in screening a patient perioperatively to determine a risk for multiple complications during a surgical procedure.

3. I have been in the practice of Anesthesiology and Critical Care Medicine for 26 years. During this entire time, and well before, the overriding mission of anesthesiologists, surgeons and other caregivers in the perioperative period has been to reduce the risk of adverse outcomes to the minimum for each patient. As well, it has long been recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery. Despite this heightened level of vigilance, and intense focus on a shared mission, no one taught or suggested perioperative genomic profiles before the present patent application.

4. Prior to the perioperative genomic profiles of the present patent application, surgeons and anesthesiologists were highly motivated to detect multiple risks for complications during a surgical procedure associated with genetic variations. For example, every patient is asked whether any family members may have had complications with surgery and anesthesia, and the patient's answer is recorded on a pre-operative checklist. Nevertheless, those of ordinary skill in the art *i.e.*, anesthesiologists and surgeons, did not arrive at the solution of the presently claimed invention. Thus, the perioperative genomic profiles of the present patent application clearly fulfill a long felt, but hitherto unmet need.

5. I have participated in a recently completed NIH-funded, prospective, multi-center investigation in which perioperative genomic profiles including alleles in *BChE, CYP2D6, MTHFR, MTR, MTRR, CBS, FII, FV, B 2AR, HBB, ApoE, MYH7, FII, FV, TPMT, CCR5, TNF a , TNF b , CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, ABC, ACE, Gender,* and *ABO*, were generated in 450 patients undergoing surgery using the technology described in the present patent application. This NIH grant focused upon the long felt but unmet needs in detection of genetic susceptibilities in the time before, during and after surgery and anesthesia.

6. Surprisingly, even after polymorphisms in non-pathogenic alleles (*i.e.*, the ABO blood group and gender-specific alleles) were withdrawn from analysis, 391 of 450 patients were found to be mutant homozygotes at 1 or more loci, with a mean number of 2 mutant homozygous loci per patient. In turn, a mean of 11 mutant alleles in aggregate (*i.e.*, homozygous plus heterozygous mutant polymorphisms) per patient were observed at loci comprising the perioperative genomic panel. These unexpected results demonstrate that significant genetic heterogeneity is present in most patients in advance of surgery that is not accounted for using contemporary tools for detection, *e.g.*, a family history check-box. Without question, the perioperative genomic profiles of the present patent application will avoid many deleterious outcomes, and save lives.

7. I am aware that the perioperative genomic profiles of the present patent application have been considered obvious by the United States Patent Office in the light of numerous separate references brought together for the first time in the present application. However, if the perioperative genomic profiles of the present patent application were obvious, the ordinary

practitioner would have arrived at the claimed combinations in view of long felt and unmet needs to directly identify genetic predispositions before, during and after surgery. No person having ordinary skill in the art, or even extraordinary skill, took this step before the claimed invention was made.

The undersigned declares further that all statements made herein of his own knowledge are true, and all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are so made punishable by fine or imprisonment, or both, under §101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: June 10th, 2007 Signed: _____
Douglas Baird Coursin M.D.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan	
Serial No.:	09/976,423	Group No.: 1634
Filed:	10/21/2001	Examiner: J.A.. Goldberg
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**	

DECLARATION OF KIRK HOGAN, M.D., UNDER 37 C.F.R. §1.132

EFS Web Filed
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Examiner,

I, Kirk Hogan M.D., do hereby declare as follows:

1. I, Kirk Hogan, am the inventor of the subject matter embodied in the above-identified patent application.

2. I am a licensed and board-certified anesthesiologist, and am a Professor in the Department of Anesthesiology at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin.

3. As an instructor and licensed and board-certified practitioner, I am knowledgeable about the practice of anesthesiology.

4. I have been a teacher of anesthesiology for over 20 years, and have participated in the training of over 100 anesthesiologists.

5. For many decades before the perioperative genomic profile kits of the present patent application, anesthesiologists were highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations. Nevertheless, anesthesiologists did not arrive at the kits of the presently claimed invention. Thus, the perioperative genomic profile kits of the present patent application clearly fulfill a long felt, but hitherto unmet need.

6. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of single polymorphisms, single genes or single diseases.

7. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of single polymorphisms, single genes or single diseases.

8. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill was not aware of kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases.

9. Prior to the perioperative genomic profile kits of the present patent application, the anesthesiologist of ordinary skill did not use kits for genomic analysis of multiple polymorphisms, multiple genes or multiple diseases.

11. While the anesthesiologist of ordinary skill has for many decades recognized that inborn predispositions are significant contributors to morbidity and mortality in the interval surrounding surgery, anesthesiologists of ordinary skill could not have combined the claimed elements because they lacked the requisite appreciation of the technical knowledge to arrive at the perioperative genomic profile kits of the presently claimed invention as a solution to the problems addressed by the presently claimed invention.

The undersigned declares further that all statements made herein of his own knowledge are true, and all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are so made punishable by fine or imprisonment, or both, under §101 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: December 17, 2007 Signed: K Hogan

X. RELATED PROCEEDINGS APPENDIX

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KIRK HOGAN

Appeal No. 2006-1517
Application No. 09/976,423

ON BRIEF

Before BARRY, ADAMS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to kits for determining risk of surgery- or anesthesia-related complications. The examiner has rejected the claims as based on new matter, anticipated, and obvious in view of the prior art. We have jurisdiction under 35 U.S.C. § 134. We reverse all of the rejections.

Background

"Although surgery saves many lives, surgical complications result in many instances of mortality and morbidity. Complications related to surgery and anesthesia include infections, excessive blood loss, thrombosis, nausea and vomiting, and anesthesia reactions." Specification, page 1.

Mutations in several genes have been linked to increased risk of surgery- and anesthesia-related complications including malignant hyperthermia, sepsis, and possible toxicity of anesthetics and other drugs. See page 2, lines 3-4 and 22-24; page 2, line 27 to page 3, line 2; and page 3, lines 12-13.

The specification discloses "a kit for generating a perioperative genomic profile for a subject, comprising a reagent capable of detecting the presence of a variant allele of two or more genes markers [sic] selected from [particular genes]; and instructions for using the kit for generating the perioperative genomic profile for the subject." Page 6, lines 15-20.

"In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP [single nucleotide polymorphism; page 28, line 19] or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease). . . . Thus, . . . the clinician, who is not likely to be trained in genetics or molecular biology, need not understand the raw data of the genomic profile. The data is presented directly to the clinician in its most useful form." Page 50, lines 8-17.

"For example, in some embodiments . . . , a sample is obtained from a subject and submitted to a genomic profiling service (e.g., clinical lab at a medical facility, genomic profiling business, etc.) to generate raw data. . . . Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo. The genomic profile data is then prepared in a format suitable for

interpretation by a treating clinician. For example, rather than providing raw sequence data, the prepared format may represent a risk assessment for various treatment options." Page 50, line 22, to page 51, line 10.

Discussion

1. Claim construction

Claims 72-107 are pending and on appeal. Claims 72 and 106 are representative and read as follows:

> 72. A kit for generating a perioperative genomic profile for a subject, comprising:
>
> a) reagents configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ so as to generate a genomic profile for use in selecting a perioperative course of action for said subject; and
>
> b) a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents.
>
> 106. A perioperative genomic profile kit having component parts configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, said subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure, are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRRR, CBS, TNFα and TNFβ, so as to generate a genomic profile for use in selecting a perioperative course of action for said subject and thereby providing a subject-specific clinical pathway for said subject, comprising information to optimize perioperative care that, based at least on the presence or absence of said variant alleles of two or more genes associated with two or more conditions selected from the group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ measured by said kit, directs a user to a specific clinical pathway of medical intervention for said subject.

Thus, claim 72 is directed to a kit comprising "reagents" and "a computer program." The claim specifies that the reagents in the kit are "configured such that when exposed to a sample containing target nucleic acid from a perioperative subject, . . . [they] are sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from [a group of specific genes]."

As we interpret the claim language, it requires reagents that are sufficient to detect the presence or absence of variant alleles in at least two of the recited genes when exposed to a sample containing a target nucleic acid. That is, the reagents in the kit can be combined with a sample from a perioperative subject and processed to detect the presence of variant alleles in the specified genes, without the addition of other reagents. This interpretation is required by the claim language: if reagents not included in the kit were required to detect the presence of variant alleles in the recited genes, then the kit would not comprise reagents "sufficient to detect" those alleles.

The other passages in part (a) of claim 72 do not constitute limitations of the claimed kit. The passage stating that the "subject [is] a patient scheduled for a surgical procedure that has not yet completed said surgical procedure" recites nothing more than an intended use of the claimed kit. That is, the specification states that the kit is intended to be used shortly before or during surgery (see page 9, lines 3-11) but that intended use does not limit the components of a kit: the same components would be required to detect the presence of the recited alleles regardless of whether the kit was used perioperatively.

In addition, the passage stating that the reagents "generate a genomic profile for use in selecting a perioperative course of action for said subject," merely recites the intended outcome of using the regents. The specification defines "genomic profile" as "a set of information about a given 'subject's' genes (e.g., the presence or absence of a specific set of mutations or 'SNPs')." Page 27, lines 13-14. Thus, the "genomic profile" recited in the claims refers simply to the data showing the presence or absence of the recited variant alleles, and reagents that are sufficient to detect alleles in at least two of the recited genes are therefore, by definition, capable of generating a genomic profile.

Finally, the kit defined by claim 72 comprises "a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents."

Claim 106 is similar to claim 72 in that it requires the same reagents (which are termed "component parts" in claim 106). As with claim 72, the claim language stating that the "subject [is] a patient scheduled for a surgical procedure that has not yet completed said surgical procedure" recites nothing more than an intended use of the claimed kit, and does not further limit the claim. Likewise, the recitation "so as to generate a genomic profile" also does not further limit the claim, because detecting the presence or absence of alleles in at least two of the recited genes by definition generates a genomic profile.

Finally, the claim language following "so as to generate a genomic profile" recites nothing more than the intended use of the genomic profile that is to be generated by the kit, and does not further limit the claimed kit. That is, the kit requires regents ("component parts") sufficient to detect polymorphisms in at least two of the recited genes, thereby generating a genomic profile, but the reagents that are capable of

detecting those alleles are the same regardless of whether the resulting genomic profile is used as recited in claim 106; the intended use language at the end of the claim therefore does not constitute a structural limitation of the claimed kit.

Claim 106 differs from claim 72 in that it does not require the claimed kit to comprise a computer program in addition to the component parts that detect the presence of variant alleles.

2. Written Description

The examiner rejected claims 72-105 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description; that is, being based on new matter. The examiner argued that "the specification does not describe or discuss 'a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents." Examiner's Answer, paragraph bridging pages 3 and 4. See also page 6: "The concept of 'a computer program comprising instructions which direct a processor to analyze data derived from use of said reagents' does not appear to be part of the originally filed invention."

However, on page 4 of the Examiner's Answer, the examiner quotes the following passage from the specification: "In some embodiments, a computer-based analysis program is used to translate the raw data generated by the genomic profile (e.g., the presence or absence of a given SNP or mutation) into data of predictive value for the clinician (e.g., probability of abnormal pharmacological response, presence of underlying disease, or differential diagnosis of known disease)" (emphases added). While this passage does not use precisely the same words as claim 72, we agree with Appellant that it reasonably describes the limitation recited in the claim.

The examiner also rejected the claims because "[t]here is no disclosure in the instant specification of a kit comprising reagents and a computer program." Examiner's Answer, page 4. See also page 5 ("there are no teachings of a computer program within a kit").

Again, however, we agree with Appellants that the specification describes the combination of a computer program and allele-detecting reagents, although not precisely in the terms used in the claims. The specification describes kits comprising reagents capable of detecting variant alleles of various genes (see, e.g., page 6, lines 15-20) and describes a "computer-based analysis program . . . to translate the raw data" generated by such kits (page 50, lines 8-12).

Moreover, the specification states that "Figure 2 illustrates the transformation of a sample . . . into data useful for the clinician." Page 50, lines 21-22. "[A] sample is obtained from a subject and submitted to a genomic profiling service (e.g., clinical lab at a medical facility, genomic profiling business, etc.) to generate raw data. . . . Once received by the genomic profiling service, the sample is processed and a genomic profile is produced (i.e., genomic data), specific for the medical or surgical procedure the subject will undergo." Page 50, line 22 to page 51, line 7.

The specification also contemplates that the party generating the genomic profile from the sample will process the data into a more easily understood format. See page 51, lines 8-15: "The genomic profile data is then prepared in a format suitable for interpretation by a treating clinician. For example, rather than providing raw sequence data, the prepared format may represent a risk assessment for various treatment options. . . . [I]n some embodiments, the genomic profiling service generates a report

that can be printed for the clinician . . . or displayed to the clinician on a computer monitor."

In our view, these disclosures reasonably support the concept of combining reagents for detecting variant alleles with a computer program to analyze data indicating the presence or absence of such variant alleles. Adequate written description does not require literal support in the specification: "In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue." Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Adequate written description requires only a disclosure that conveys with reasonable clarity to those skilled in the art that the inventor was in possession of the invention. See id.

In this case, we conclude that the examiner has not adequately explained why the description provided by the specification would be considered inadequate, by those skilled in the art, to show possession of the instanty claimed kit. We therefore reverse the rejection based on the first paragraph of 35 U.S.C. § 112.

3. Anticipation

The examiner rejected claims 72-105 under 35 U.S.C. § 102(b) as anticipated by Applied Biosystems,[1] and rejected claims 106 and 107 as anticipated by Perkin Elmer.[2]

With regard to Applied Biosystems, the examiner reasoned that

> Applied Biosystems provides several products which are packaged for distribution, kits, which allow for detecting the presence of variant alleles of two or more genes. Applied Biosystems products for sale include: a DNA analysis system; software for genetic analysis; . . . PRISM Ready reaction

[1] Sales catalog of Applied Biosystems, Inc., pp. 135-157 and 160-164 (1993)
[2] PCR Systems, Reagents & Consumables catalog, Perkin Elmer, pp. 15-18 (1995)

> cycle sequencing kits; AmpliTaq Cycling Sequencing Kits; . . . etc. Each of these products is capable of detecting the presence of variant alleles of two or more genes. Applied Biosystems teaches numerous computer programs which are sold with the DNA analysis system, for example.

Examiner's Answer, page 7. Similarly, with respect to Perkin Elmer, the examiner reasoned that

> Perkin Elmer provides several products which are packaged for distribution, kits, which allow for detecting the presence of variant alleles of two or more genes. First, Perkin Elmer teaches the GeneAmp PCR Reagent Kit with AmpliTaq DNA polymerase. . . . This kit provided by Perkin Elmer contains reagents which allow for detection of variant alleles of two or more genes.

Id., page 9.

Appellant argues that "the Examiner has ignored [certain] claim elements entirely i.e., reagents **sufficient** to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from the specified group consisting of BChE, CYP2D6, F5, F2, CACNAIS, MTHFR, MTR, MTRR, CBS, TNFα and TNFβ. . . . It is a matter of simple fact that the 1993 Applied Biosystems Product Catalog is insufficient, standing alone, to detect the alleles of the perioperative genomic profile kits of the present invention without more, i.e., specific reagents to do so." Appeal Brief, page 24. See also Reply Brief, page 11 (arguing that Perkin Elmer does not teach kits comprising parts that are "sufficient to detect the presence or absence of variant alleles in two or more genes associated with two or more conditions selected from" the recited genes).

We agree with Appellant that neither Applied Biosystems nor Perkin Elmer disclose the kits defined by instant claims 72 and 106. As Appellant points out, the claimed kits must include reagents (or component parts) "sufficient to detect" variant

alleles in at least two of the recited genes. We agree with this interpretation of the claims.

None of the kits disclosed by either Applied Biosystems or Perkin Elmer include reagents that are specific to any of the genes recited in claims 72 and 106. The kits disclosed in the references contain reagents for performing a polymerase chain reaction (PCR) process or for carrying out DNA sequencing. Granted, the kits disclosed by the references would allow a skilled worker to amplify and sequence any given DNA fragment, given primers specific to the desired fragment. What is missing from the references, however, is a disclosure of primers specific to any of the genes recited in claims 72 and 106.

"[A]nticipation requires that all of the elements and limitations of the claim are found within a single prior art reference." Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991). Applied Biosystems does not disclose a product meeting all the limitations of claim 72 and Perkin Elmer does not disclose a product meeting all the limitations of claim 106. We therefore reverse the rejections based on Applied Biosystems and Perkin Elmer.

4. Obviousness

The examiner rejected claims 106 and 107 under 35 U.S.C. § 103(a) as obvious in view of either Rosen[3] and Ahern[4] or Tarkowski[5] and Ahern. The examiner noted that "Rosen teaches [that] genotyping of selected loci of the TNF-alpha and TNF-beta

[3] Rosen, U.S. 2002/0119468 A1, published August 29, 2002
[4] Ahern, "Biochemical, reagent kits offer scientists good return on investment," The Scientist, Vol. 9, p. 20 (1995)
[5] Tarkowski et al., "TNF gene polymorphism and its relation to intracerebral production of TNF α and TNF β in AD," Neurology, Vol. 54, pp. 2077-2081 (2000)

coding regions was performed by PCR amplification and restriction digestion," (Examiner's Answer, page 11) and that "Tarkowski teaches analyses of TNFalpha and TNFbeta gene polymorphism[s]," using PCR and restriction enzyme digestion. Id., page 13.

The examiner acknowledged that neither Rosen nor Tarkowski discloses packaging the TNF-specific reagents in a kit, but relied on Ahern to suggest that limitation: "Ahern teaches reagent kits offer scientists good return on investment. Ahern teaches kits save time and money because the kits already come[ ] prepared." Examiner's Answer, pages 11 and 13.

The examiner concluded that it would have been prima facie obvious to package the reagents taught by Rosen into a kit because Rosen "teaches mutations at –308 [of TNF-α] and aa13 and aa26 [of TNF-β] which are associated with predisposition to liver rejection." Id., page 12. Similarly, the examiner concluded that it would have been obvious to package Tarkowski's reagents in a kit because "Tarkowski specifically teaches two polymorphic genes which are associated with AD [Alzheimer's disease]." Id., page 13.

Appellant argues that the examiner's rejection should be reversed because, among other things, the cited references do not provide a sufficient suggestion or motivation to combine their teachings. See the Reply Brief, pages 13-15 and 17-19.

We agree with Appellant that the references relied on by the examiner do not support a prima facie case of obviousness. "[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior

art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted). "[T]he 'motivation-suggestion-teaching' test asks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims." In re Kahn, 441 F. 3d 977, 988, 78 USPQ2d 1329, 1337 (Fed. Cir. 2006).

In this case, the examiner has not adequately explained why a person of ordinary skill in the art would have been found it obvious to package the reagents taught by either Rosen or Tarkowski into a kit that would meet the limitations of instant claim 106. Rosen teaches a method of identifying organ donors having livers less likely to be reinfected by hepatitis C virus (HCV). See ¶ 0007. Rosen teaches that the TNF-α gene has a polymorphic position at –308: the allele TNF308.1 has a G at this position while the allele TNF308.2 has an A. See ¶ 0035. Rosen also teaches that "[k]nown TNF-β polymorphisms include the TNFc locus, the aa13 locus, the aa26 locus and the NcoI locus." See ¶ 0028.

Rosen amplified and sequenced polymorphic positions in the TNF-α and TNF-β genes and found that livers from donors with the TNF308.2 allele in the TNF-α gene were reinfected by HCV more often and more severely than livers from donors with the TNF308.1 allele. See ¶ 0066. By contrast, "[t]here was no correlation between the TNF-β alleles and time to recurrence, severity of recurrence or the prevalence of rejection." ¶ 0067.

Thus, Rosen teaches that a polymorphism in the TNF-α gene is informative in predicting which livers are more likely to be reinfected in HCV-infected patients, but that polymorphisms in the TNF-β gene are not. In view of Rosen's teaching that TNF-β-specific primers are useless for predicting likelihood of HCV reinfection, we conclude that the examiner has not adequately explained why Rosen would have led a person skilled in the art to package primers specific for both TNF-α and TNF-β into a kit.

Like Rosen, Tarkowski teaches PCR primers for amplifying parts of the TNF-α and TNF-β genes. See pages 2078-2079. Tarkowski analyzed the association between aspects of Alzheimer's disease (AD) and polymorphisms in the TNF-α and TNF-β genes, but concluded that "the levels of these cytokines did not differ significantly in patients displaying different alleles of the TNF gene." Abstract. See also page 2080, right-hand column, second full paragraph:

> [T]he frequencies of TNFα1 versus TNFα2 alleles did not differ between patients with AD and control subjects, suggesting a lack of association between TNF polymorphism and the susceptibility for AD. The intrathecal TNFα levels or the degree of cognitive deficit did not differ significantly between the groups of AD patients with different TNFα or TNFβ gene polymorphism, suggesting a lack of association between TNF polymorphism and the clinical severity of AD.

(Emphases added.)

Thus, Tarkowski teaches that the TNF-α and TNF-β polymorphisms that were examined were not associated with either the susceptibility to or the clinical severity of Alzheimer's disease in potential patients. In view of this teaching, we conclude that the examiner has not adequately explained why Tarkowski would have led a skilled worker to package the TNF-α- and TNF-β-specific primers disclosed by Tarkowski into a kit.

Other Issue

This application is said to be "a continuation-in-part of co-pending U.S. application serial number 09/613,887" (specification, page 1), which is the subject of appeal number 2006-1560. The claims in that application are directed to a method, rather than a kit, for perioperative screening. The examiner rejected the claims as obvious in view of, among other references, Pharmacogenetics[6] and AAS.[7]

AAS discloses that different alleles of the BChE gene affect patients' reactions to succinylcholine (page 139, left-hand column), that "careful DNA analysis is really the only way to establish individual BChE genotypes" (page 140, right-hand column), that "[w]e have been able to sequence the entire BCHE coding region and consider all the possible structural mutations using PCR amplification" (id.), and that "anesthesiologists need to keep up to date about" the application of molecular biology tests to BChE variants (sentence bridging pages 140 and 141).

Pharmacogenetics discloses that cytochrome P4502D6 (CYP2D6) in involved in mediating drug biotransformation (page 309), including the transformation of codeine to its active form (page 317, left-hand column), and that by combining "rapid and specific PCR-based allele-specific amplification tests . . . [with] XbaI RFLP analysis, about 95 percent of all mutant alleles of CYP2D6 could be identified, allowing for the prediction of over 90 percent of PM [poor metabolizer] phenotypes" (page 314, right-hand column).

[6] The reference is cited as "Pharmacogen[e]tics, Chapter 4, pp. 309-326" in the Information Disclosure Statement received in application 09/613,887 on April 6, 2001 (reference number 202 in the IDS).
[7] La Du, "Butyrylcholinesterase variants and the new methods of molecular biology," Acta Anaesthesiologica Scandinavica, Vol. 39, pp. 139-141 (1995)

On return of this application, the examiner should consider whether the references cited in application 09/613,887, together with the prior art of record, would support a prima facie case of obviousness with respect to any of the claims in the instant application.

REVERSED

Lance Leonard Barry)
Administrative ~~Patent Judge~~)
)
)
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Donald E. Adams)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte KIRK HOGAN

Appeal No. 2006-1560
Application No. 09/613,887

ON BRIEF

Before ADAMS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of screening patients for risk of surgical complications, which the examiner has rejected a obvious. We have jurisdiction under 35 U.S.C. § 134. We affirm the rejection.

Background

"Although surgery saves many lives, surgical complications result in many instances of mortality and morbidity. Complications related to surgery and anesthesia include infections, excessive blood loss, thrombosis, nausea and vomiting, and anesthesia reactions." Specification, page 1.

"One anesthesia-related complication is malignant hyperthermia (MH). MH is an autosomal dominant trait that causes a severe, uncontrollable fever when anesthesia is administered." Id. "[M]uscle relaxants commonly given in conjunction with anesthesia, such as succinylcholine or mivacurium, can cause prolonged paralysis and apnea in a patient after the patient has awoken from anesthesia. The paralysis, caused by mutations in the butyrylcholinesterase gene (BChE), is inherited as an autosomal recessive trait.. . . In addition, subjects with mutations in Cytochrome P450 enzymes . . . can have adverse reactions due either to the inability to activate or metabolize certain drugs (e.g., morphine derivatives and anti-dysr[hy]thmics). Complications can be avoided by substituting other medications or adjusting dosage." Page 2.

Despite these known, genetically determined susceptibilities to side effects of anesthesia, however, "the current state of the surgical field is to reduce or eliminate perioperative testing." Specification, page 5. "[T]he current procedure is simply to ask a patient if they have had any previous difficulties with anesthesia or surgery. . . . The use of laboratory tests for relatively healthy patients has generally been reduced or eliminated. Reasons for elimination include the cost of screening tests, inaccuracy and lack of specificity, [and] uncertainty as to how to alter treatment course of action in response to results." Id.

The specification discloses "methods for perioperative genomic screening of subjects, in particular . . . perioperative screening for markers indicative of responses to anesthesia and other perioperative or operative treatments and procedures." Page 3. "Markers for inclusion are selected for their accuracy, specificity, and predictive value. The perioperative profiles . . . allow for the individualization of treatment options for each

subject." Page 6. "Markers are also selected for which the course of action can be altered in a time and cost effective way to eliminate or reduce unwanted surgical complications. For example, a practitioner may cho[o]se a particular anesthetic or analgesic in order to avoid a life-threatening response." Id.

Discussion

1. Claim construction

Claims 74-105 are pending and on appeal. Claim 74 is representative and reads as follows:

74. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample form a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complication during said surgical procedure.

"It is axiomatic that, in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Sneed, 710 F.2d 1544, 1548, 218 USPQ 385, 388 (Fed. Cir. 1983) (citation omitted).

In addition, "while it is true that claims are to be interpreted in light of the specification and with a view to ascertaining the invention, it does not follow that

limitations from the specification may be read into the claims." Sjolund v. Musland, 847 F.2d 1573, 1581, 6 USPQ2d 2020, 2027 (Fed. Cir. 1988) (emphasis in original). On the contrary, "the claims define the invention. . . . [L]imitations from the specification are not to be read into the claims." Id. at 1582, 6 USPQ2d at 2027.

Here, claim 74 is directed to a method the comprises obtaining a sample from a patient and testing the sample for the presence of "two or more nucleic acid genetic markers in two or more genes associated with two or more conditions." The results of the testing form the basis for "determining a risk for complications during said surgical procedure"; thus, the "conditions" recited in the claim are those associated with "a risk for complications during a surgical procedure associated with known genetic variations," as recited in the preamble.

Claim 74 also states that the results of the "assay for detecting two or more nucleic acid genetic markers . . . generate[s] a genomic profile." The specification states that "a 'genomic profile' refers to a set of information about a given 'subject's' genes (e.g., the presence or absence of a specific set of mutations or 'SNPs')." Page 23, lines 7-9. Thus, the "genomic profile" recited in claim 74 merely refers to the data resulting from the recited "assay for detecting two or more genetic markers."

Claim 74 also states that the genomic profile is "for use in selecting a perioperative course of action." This claim language, however, merely recites an intended use for the data resulting from the assay step in the claim. "An intended use or purpose usually will not limit the scope of the claim because such statements usually do no more than define a context in which the invention operates." Boehringer Ingelheim Vetmedica v. Schering-Plough Corp., 320 F.3d 1339, 1345, 65 USPQ2d

1961, 1965 (Fed. Cir. 2003). Therefore, claim 74 is not limited to a process that includes selecting a perioperative course of action based on the results of the assay.

2. Obviousness

The examiner rejected claims 74-105 under 35 U.S.C. § 103 as obvious in view of Miller,[1] Quane[2] or AAS,[3] La Du[4] or Pharmacogenetics,[5] Evans[6] or Poort,[7] Hoon,[8] and Hacia.[9]

The examiner characterized Miller as teaching "screening a patient preoperatively to determine a risk for complications during a surgical procedure," although she acknowledged that Miller does not teach testing for "two or more known genetic variations associated with two or more conditions." Examiner's Answer, page 4.

However, the examiner cited Quane for its disclosure of "novel common mutations in [the] ryanodine receptor gene (RYR1) in malignant hyperthermia (MH)" and noted that Quane teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." Id. The examiner

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[1] Anesthesia, Vol. 2, Miller (ed.), pp. 1323-1333, Churchill Livingstone, NY (1981)
[2] Quane et al., "Detection of a novel common mutation in the ryanodine receptor gene in malignant hyperthermia: implications for diagnosis and heterogeneity studies," Human Molecular Genetics, Vol. 3, pp. 471-476 (1994)
[3] La Du, "Butyrylcholinesterase variants and the new methods of molecular biology," Acta Anaesthesiologica Scandinavica, Vol. 39, pp. 139-141 (1995)
[4] La Du et al., "Proposed nomenclature for human butyrylcholinesterase genetic variants identified by DNA sequencing," Cellular and Molecular Neurobiology, Vol. 11, pp. 79-89 (1991)
[5] The reference is cited as "Pharmacogen[e]tics, Chapter 4, pp. 309-326" in the Information Disclosure Statement received April 6, 2001 (reference number 202 in the IDS).
[6] Evans et al., "Pharmacogenomics: Translating functional genomics into rational therapeutics," Science, Vol. 286, pp. 487-491 (1999)
[7] Poort et al., "A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis," Blood, Vol. 88, pp. 3698-3703 (1996)
[8] Hoon et al., U.S. Patent 6,057,105, issued May 2, 2000.
[9] Hacia, "Resequencing and mutational analysis using oligonucleotide microarrays," Nature Genetics Supplement, Vol. 21, pp. 42-47 (1999)

also cited AAS for its disclosure that certain variants of the butyrylcholinesterase (BChE) gene cause patients to react differently to the muscle relaxant drug succinylcholine. Id. The examiner also noted AAS's advice that anesthesiologists need to keep up to date about the application of molecular biology tests to BChE variants. Id.

The examiner cited La Du, Pharmacogenetics, and Evans as disclosing genetic variations that are associated with abnormal responses to drugs. See the Examiner's Answer, pages 6-7:

> La Du . . . teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. . . .
>
> Pharmacogenetics teaches polymorphisms of desbrisoquine [sic] hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. . . . Codeine is [an] ineffective analgesic in the 5-10% of the population who have a PM [poor metabolizer] phenotype.
>
> Evans . . . teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. . . . Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. . . ."

The examiner cited Poort's disclosure that a "20210 AG gen[ot]ype of the prothrombin gene . . . is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedure or trauma." Id., page 7. Finally, the examiner cited Hoon as "teach[ing] the benefits of using multiple markers in detection assays," id., and Hacia as "teach[ing] mutational analysis using oligonucleotide microarrays . . . allow[ing] for unprecedented throughput in mutational analysis with a high degree of accuracy." Id., page 8.

We agree with the examiner that the cited references would have made the method of claim 74 prima facie case obvious. In particular, Quane, AAS and Pharmacogenetics disclose specific mutations that are associated with abnormal responses to commonly used drugs, and which can be identified in patients by genetic analysis.

Quane teaches that malignant hyperthermia (MH) is a potentially fatal complication "triggered in susceptible people by all commonly used inhalation anaesthetics" (abstract), that susceptibility to MH can be predicted by testing strips of muscle tissue in vitro, and that "[o]nce an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided" (page 471, right-hand column).

Quane also discloses that certain mutations in the ryanodine receptor gene (RYR1) are associated with susceptibility to MH: "a point mutation . . . that results in an Arg to Cys substitution at position 615 . . . has been found in 3-5% of human MH families investigated and is the most common MHS [MH susceptible; see page 471, right-hand column] mutation known to date. More recently, we reported a second MHS mutation, namely an Arg to Cys substitution at position 163 which accounts of 2-3% of MHS cases." Paragraph bridging pages 471-472 (reference numbers omitted). Quane reports that another mutation, Gly341Arg, "accounts for approximately 10% of Caucasian MHS cases." Abstract. Finally, Quane states that the Gly341Arg mutation "satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means." Page 474, left-hand column.

AAS teaches that genetic variation in the butyrylcholinesterase (BChE) gene causes patients to react differently to the muscle relaxant succinylcholine: "[T]he better known variants [are known as] A=atypical (dibucaine resistant), F=fluoride resistant, and S=silent (no significant activity)." Page 139, right-hand column. AAS states that succinylcholine (SC) is metabolized quickly in normal patients, so that in patients lacking functional BChE, the standard dose "represents an enormous overdosing" and is "potentially toxic." Page 139, left-hand column.

AAS also teaches that "[a]bout 16 different DNA mutations causing the silent phenotype have been uncovered, so far" (page 140, left-hand column, first full paragraph) and that "[w]e have been able to sequence the entire BCHE coding region and consider all the possible structural mutations using PCR amplification" (page 140, end of the paragraph bridging the columns). Finally, AAS notes that "the principles of molecular biology and their application to BChE variants [have been] well illustrated . . ., and anesthesiologists need to keep up to date about these applications. Other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years." Paragraph bridging pages 140 and 141.

Pharmacogenetics teaches that the enzyme cytochrome P4502D6 (also known as CYP2D6) is involved in biotransformation of the antihypertensive agent debrisoquine and "at least 30 other agents." Page 310, first and last paragraphs. "[A]pproximately five to ten percent of the individuals in healthy Caucasian populations are distinguishable as phenotypically 'poor metabolizers' (PM)." Page 310, left-hand column, first paragraph. "Codeine and encainide represent examples of drugs that

require metabolic activation by CYP2D6 before certain of their therapeutic effects can be fully realized. Thus, for these drugs it is the PM subjects who may experience therapeutic failure. . . . [C]odeine is therefore an ineffective analgesic in the 5 to 10 percent of the population who have the PM phenotype." Page 317, left-hand column, first full paragraph.

Pharmacogenetics also discloses "the development of rapid and specific PCR-based allele-specific amplification tests to detect the presence of the D6-A and D6-B mutant alleles, and more recently the putative D6-C allele. By combining these with the . . . XbaI RFLP analysis, about 95 percent of all mutant alleles of CYP2D6 could be identified, allowing for the prediction of over 90 percent of PM phenotypes." Page 314, right-hand column, first full paragraph.

Evans and Hacia discuss methods of genetic analysis. Evans states that "[s]ince the cloning and characterization of CYP2D6, human genes involved in many such pharmacogenetic traits have been isolated, their molecular mechanisms have been elucidated, and their clinical importance has been more clearly defined. . . . [T]he overall pharmacologic effects of medications are typically not monogenic traits; rather, they are determined by the interplay of several genes encoding proteins involved in multiple pathways of drug metabolism, disposition, and effects." Page 487, paragraph bridging the columns. Evans provides a list of "[e]xamples of clinically relevant genetic polymorphisms influencing drug metabolism and effects." Table 1.

Evans also discloses that "technology will soon make it feasible to use molecular diagnostics to more precisely select medications and dosages that are optimal for individual patients. In this regard, automated systems are being developed to

determine an individual's genotype for polymorphic genes that are known to be involved in the pathogenesis of their disease, in the metabolism and disposition of medications, and in the targets of drug therapy." Paragraph bridging pages 490 and 491. Evans provides an example of a DNA array for the "detection of functionally important mutations in genes that are important determinants of drug effects"; the exemplified array includes "genes that could influence a patient's response to chemotherapy for acute lymphoblastic leukemia." See Figure 3.

Hacia states that "[o]ligonucleotide array-based detection of known genomic DNA sequence variations was first reported in 1989. . . . Advanced oligonucleotide array manufacturing processes have opened the way to evaluating more complex systems. Arrays of 1,480 oligonucleotide probes . . . were designed to detect 37 known mutations in the coding region of CFTR, as well as all possible single-nucleotide substitutions." Page 42, right-hand column. Hacia also teaches that "[a]mong the greatest strengths of array-based mutational analysis is the ability to detect specific sequence changes of interest. Once specific hybridization patterns or 'signatures' of large numbers of mutant alleles of interest are known, it will be possible to search for those signatures in many different samples simultaneously." Page 45, right-hand column.

We agree with the examiner that these disclosures, viewed collectively by a person of ordinary skill in the art, would have made obvious the method defined by claim 74.[10] That is, it would have been obvious to a person of skill in the art to test a patient who was scheduled for surgery to determine whether the patient had any of the

[10] In our view, the other references cited by the examiner are essentially cumulative to those discussed above.

genetic polymorphisms known to be associated with specific surgery- or anesthesia-related complications, including the RYR1 mutations discussed by Quane, the BChE mutations discussed by AAS, and the CYP2D6 mutations discussed by Pharmacogenetics. The skilled artisan would have found it obvious to conduct such testing (using, for example, DNA hybridization techniques such as those disclosed by Evans and Hacia) in order to avoid the known risk of side-effects, including death, that were likely to occur when patients having a particular genetic make-up were given particular drugs.

Appellant argues that the examiner has not adequately established that a person of ordinary skill in the art would have been motivated to combine the teachings of the cited references. See the Appeal Brief, pages 15-21. Appellant's argument, however, focuses on the teachings of Quane in isolation. A proper obviousness analysis must consider all of the teachings of the prior art, viewed from the perspective of a person of ordinary skill in the art. For the reasons discussed above, we conclude that the references cited by the examiner would have suggested the method of claim 74 to those of ordinary skill in the art.

Appellant also argues that he has provided evidence that rebuts the reasoning relied on by the examiner by showing that "ordinary artisans did not agree with the Examiner's suppositions regarding the obviousness of perioperative genomic profiles." Appeal Brief, page 22. Appellant argues that the APSF Grant Review[11] is evidence of

[11] Appellant states in the declaration filed under 37 CFR § 1.132 on February 8, 2002, that he "filed a grant application entitled 'Perioperative Genomic Profiles' with the Anesthesia Patient Safety Foundation (APSF). . . . The grant application described the subject matter of the present invention and was rejected." ¶ 11. Neither the grant application nor the rejection letter appear to be in the record, although

the nonobviousness of the claimed method, because skilled artisans described it a "tak[ing] the issues of patient safety in a new direction," and stated that "[t]he direction of anesthetic evaluation is presently to not routinely do any preoperative studies." Appeal Brief, page 23.

Appellant argues that Gregory[12] and Kirby[13] teach away from the claimed method in their statements that "routine screening tests are of little value" (Gregory) and "[t]here are abundant data supporting the concept that routine laboratory screening tests are not cost-effective in the asymptomatic patient" (Kirby). Appeal Brief, page 24.

Appellant also argues that Hopkins[14] is evidence that "the Examiner's premises concerning the motivations of the ordinary artisan are in clear error," in that Hopkins states that "[t]he complexity of the molecular genetics of MH described above precludes DNA-based diagnosis at present." Appeal Brief, page 26.

Finally, Appellant argues that his second declaration under 37 CFR § 1.132 (dated July 15, 2002) and the reference attached thereto,[15] are evidence of nonobviousness, in that the "Practice Advisory for Preanesthesia Evaluation . . . does not provide guidelines for selecting markers useful for perioperative genetic testing, and does not advocate, consider or even mention genetic testing, use of genetic markers, or generation of genomic profiles." Appeal Brief, page 27.

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we will accept Appellant's statement that the quotation in ¶ 11 of the declaration represents "the committee's comments, in full."

[12] Gregory, Pediatric Anesthesia, 4th edition, Churchill Livingstone, NY (2002). Page 184 of Gregory was attached to the declaration filed Feb. 8, 2002.

[13] Kirby et al., Clinical Anesthesia Practice, 2nd edition, W.B. Saunders Co., Philadelphia (2002). Page 12 of Kirby was attached to the declaration filed Feb. 8, 2002.

[14] Hopkins, "Malignant hyperthermia: advances in clinical management and diagnosis," Br. J. of Anaesthesia, Vol. 85, pp. 118-128 (2000)

[15] "Practice Advisory for Preanesthesia Evaluation," Anesthesiology, Vol. 96, pp. 485-496 (2002)

Appellant concludes that "this factual evidence consistently documents that at the time the invention was made, ordinary artisans did not agree with the Examiner's suppositions regarding the obviousness of perioperative genomic profiles." Appeal Brief, page 22.

While we appreciate Appellant's effort to provide evidence supporting his position, we agree with the examiner that the evidence does not overcome the prima facie case of obviousness. The APSF committee's response to Appellant's grant application is not probative of nonobviousness for two reasons. First, the grant application itself is not in the record, so we do not know how the method that was proposed in the grant, and addressed in the committee's comments, compares to the method of claim 74.

Second, and more important, the committee's comments were addressed to the cost-effectiveness of whatever method was proposed in the grant. According to Appellant's declaration (¶ 11), the committee stated that

> [T]he committee members considered the study might improve quality but the cost could be very high. As anesthesia practice has moved toward determining the ratio of quality to cost, this study seems to be going in the opposite direction.

However, whether a claimed invention would have been obvious in the § 103 sense has little to do with whether it would be economically viable in actual practice. A method can properly be considered obvious under § 103 even if it would have been more expensive than alternative methods. See In re Farrenkopf, 713 F.2d 714, 718, 219 USPQ 1, 4 (Fed. Cir. 1983):

> That a given combination would not be made by businessmen for economic reasons does not mean that persons skilled in the art would not

> make the combination because of some technological incompatibility. Only the latter fact would be relevant.

(Citing Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 1013, 217 USPQ 193, 200 (Fed. Cir. 1983).)

In this case, a person of ordinary skill in the art would have found it obvious, in view of the cited references, to test a patient for genetic markers in order to avoid known surgery- and anesthesia-related complications, even though such tests might be expensive, because those skilled in the art would have recognized that the tests were useful for diagnosing patients who were likely to suffer complications if given certain drugs.

The Kirby and Gregory textbooks also do not persuade us that the examiner's rejection is in error. The textbooks suffer from the same deficiency as the APSF committee's remarks. In addition, both textbooks address only "routine laboratory screening tests," which appear to be limited to tests such as urinalysis, hemoglobin and hematocrit. See Gregory, page 184, left-hand column. Neither reference addresses tests for genetic markers such as claimed here.

Hopkins also does not overcome the prima facie case of obviousness. It is true that Hopkins states that the "complexity of the molecular genetics of MH described above precludes DNA-based diagnosis at present [i.e., in 2000]." Nevertheless, Hopkins also states that known mutations were found in a number of MH-susceptible individuals and that "it is difficult to envisage that the mutations so far described in RYR1 do not play a role in MH." Page 125, left-hand column. In any event, Hopkins at best expresses doubt about the likelihood of successfully diagnosing malignant

hyperthermia, but it says nothing to raise doubts about genetic testing for the CYP2D6 or BChE mutations that are disclosed by Pharmacogenetics and AAS, respectively.

Finally, with respect to Appellant's rebuttal evidence, the Practice Advisory attached to Appellant's second declaration suffers from a combination of the deficiencies discussed above: it reflects the cost-benefit trade-offs of the standard of care for present-day clinical practice, which is the wrong standard for determining obviousness under § 103, and it is limited to routine laboratory tests that do not include the type of genetic testing at issue in this case.

Appellant also argues that the cited references do not teach or suggest all of the limitations of claims 74, 76, 78, 81-87, 91-94, 96, 98, 101-103, or 105. Appeal Brief, pages 12-14 and 29-30. However, we agree with the examiner that the cited references would have suggested the limitations of these claims, for the following reasons.

Appellant argues that the references cited by the examiner "fail to teach, suggest or even mention" the following limitations: from claim 74, "a genomic profile for use in selecting a perioperative course of action"; from claim 87, "a genomic profile for use in selecting a surgical treatment course of action"; from claims 94 and 101, "a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure"; and from claim 102 "an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said assay results are consulted in selecting an appropriate anesthesia treatment." Appeal Brief, pages 12-13.

We do not agree with Appellant that these claim limitations distinguish the claimed methods from that suggested by the prior art. With respect to claims 74, 87,

94, and 101, the "genomic profile . . ." claim language merely recites an intended use for the information that is produced during the claimed process. The intended use of the data does not limit the claimed process. See pages 4-5 above.

Claim 102 is somewhat different, in that it recites a step of "subjecting said subject to a surgical procedure, wherein said assay results are consulted in selecting an appropriate anesthesia treatment for said subject." Thus, claim 102 requires considering the assay results during the selection of anesthesia for a patient undergoing surgery. This limitation is suggested by the cited references. For example, Quane states that a Gly341Arg mutation in the RYR1 gene causes sensitivity to malignant hyperthermia, and that "[o]nce an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided." These disclosures would have reasonably suggested consulting the results of an assay for the RYR1 Gly341Arg mutation and avoiding anesthetics that trigger MH in patients having that mutation. Appellant's argument with respect to claims 86, 98, 103, and 105 (Appeal Brief, page 14) is unpersuasive for the same reason.

Appellant argues that the cited references do not teach or suggest assaying for "5 or more mutations," as recited in claims 84, 92, and 99, or "10 or more mutations," as recited in claims 85, 93, and 100. Appeal Brief, pages 12-13. Appellant also argues that the cited references do not suggest assaying for mutations in at least two of the specific genes recited in claims 83, 91, and 101. See id., pages 12, 13, and 30.

We do not find this argument persuasive. Quane discloses three mutations in the RYR1 gene that are associated with MH susceptibility: Arg to Cys at position 615 (paragraph bridging pages 471 and 472), Arg to Cys at position 163 (id.), and

Gly341Arg (abstract). Pharmacogenetics discloses at least three mutations associated with the "poor metabolizer" phenotype of CYP2D6 (the D6-A, D6-B, and D6-C alleles; page 314, right-hand column). AAS discloses that "about 16 different DNA mutations causing the silent phenotype have been uncovered" (page 140, first full paragraph), along with one causing the "atypical" phenotype and two causing the "fluoride-resistant phenotype" (page 140, second full paragraph).

Based on these disclosures, the skilled artisan would have found it obvious to assay for each of these mutations, which were known to be associated with aberrant drug responses. Thus, those skilled in the art would have found it obvious to assay for at total of at least ten mutations in the RYR1, BChE (butyrylcholinesterase), and CYP2D6 (debrisoquine hydroxylase) genes.

Appellant argues that the cited references do not teach or suggest the added limitations of claim 76, 78, and 96. Appeal Brief, pages 13 and 14. These claims, however, merely further limit the intended use of the information that is produced during the claimed process. Since the intended use of the data does not limit the claimed process (see pages 4-5 above), the language recited in claims 76, 78, and 96 does not distinguish the claimed methods from that suggested by the prior art.

Finally, Appellant argues that the cited references do not teach or suggest a "genomic profile [that] comprises a presymptomatic diagnosis," as recited in claim 81. Appeal Brief, page 13. This argument is also unpersuasive. As discussed above (page 4), the "genomic profile" recited in claim 74 is merely the data resulting from the recited "assay for detecting two or more genetic markers." An assay for the specific mutations disclosed in the cited references would inherently be diagnostic of, among other things,

a potential for an abnormal response to succinylcholine. As AAS states, the "genetically-determined prolonged response to SC in occasional patients is a classical example of a pharmacogenetic condition. Since these individuals . . . [do not] suffer any adverse consequences of this hereditary condition, unless SC or mivacurium is given, the condition is provoked only when the offending drug substances are administered." Page 139, left-hand column. Thus, a presymptomatic diagnosis is suggested by at least AAS.

Summary

The examiner has made out a prima facie case of obviousness, which Appellant has not effectively rebutted. The examiner's rejection is supported by a preponderance of the evidence in the record and is therefore affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Donald E. Adams)
Administrative Patent Judge)
)
)

) BOARD OF PATENT
Eric Grimes)
Administrative Patent Judge) APPEALS AND
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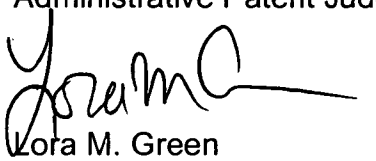
) INTERFERENCES
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XI. CONCLUSION

For the foregoing reasons, Appellants respectfully submit that the Examiner's rejection of Claims 72-112 is erroneous. Reversal of the rejections is respectfully requested. Appellants request that the Board render a decision as to the allowability of the Claims.

Respectfully submitted,

Dated: April 15, 2009

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